Biomechanical analysis of specific motor impairments contributing to early functional decline in adults living with HIV-1 infection:

A sub-study to the Cape Winelands HAART to HEART (Prevalence)/EndoAfrica study

by

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DECLARATION

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This dissertation includes one original paper published in a peer-reviewed journal. The development and writing of the chapters were the principal responsibility of myself and for each of the cases where this is not the case a declaration is included in the dissertation indicating the nature and extent of the contributions of co-authors.

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ABSTRACT

Background

HIV-1 infection has become a chronic condition. Although people living with HIV-1 infection (PLHIV) now have near-normal life expectancies, walking-related impairments remain concerning as they occur early and may lead to falls. A poor understanding remains of *how* movement patterns are affected due to a lack of biomechanical studies. Three-dimensional (3D) motion analysis can provide insight into movement patterns and assist in identifying a valid performance-based screening test for detecting early motor impairments in PLHIV.

Aim

The aim of this research was to investigate gait and balance impairments existing in PLHIV using 3D motion analysis. It further aimed to correlate 3D analysis findings (via a gait summary score), as well as self-reported function and history and fear of falling, to physical performance tests which may be considered in clinical practice to screen for early functional decline in PLHIV.

Methods

The research was divided into three parts:

Part I presented a systematic review describing objective gait and balance impairments in PLHIV. Results contributed to the theoretical groundwork for study conceptualisation and aided in selecting clinically relevant biomechanical outcomes and performance-based tests.

Part II comprised validity and reliability testing of a portable 3D gait analysis (3DGA) system, newly obtained by the motion laboratory, in 16 healthy student volunteers, as well as in eight consecutively recruited PLHIV and eight community-matched seronegative participants (SNP). The studies determined the psychometric properties of specific 3DGA outcomes to aid appropriate data interpretation in the next phase.

Part III comprised the main observational study to cross-sectionally describe key biomechanical characteristics in 50 PLHIV relative to 50 community-matched SNP (consecutively sampled). The study was conducted in a clinical setting, and performance-based tests were assessed in addition to the 3D motion analysis. Gait analysis results, fall-related outcomes and self-reported function were correlated to clinical test performance to identify the most valid performance-based screening test.

Main results

The systematic review (Part I) revealed some agreement that PLHIV walk slower and have increased centre of pressure (COP) excursions and postural reflex latencies, particularly under challenging conditions. No included studies used 3DGA. The validity and reliability studies (Part II) demonstrated that, with regular recalibration, the 3DGA system reliably measures gait biomechanics in SNP and PLHIV, except for four discrete angles. The system/model highly compares to the reference model after accounting for modelling differences. The field study (Part III) revealed that the gait of PLHIV (median age: 36.61 years) was significantly slowed and rigid relative to SNP (median age: 31.10 years). This pattern manifested when walking at a usual pace or when performing a dual task. Dual task walking further revealed joint range of motion (ROM) changes at the hip and knee in a distal-to-proximal pattern-shift. PLHIV also demonstrated increased COP excursion in dual task single-leg stance. PLHIV were significantly slower in completing the Five-Times Sit-To-Stand (5STS) Test. Slowed sit-to-stand was significantly related to gait rigidity, worse self-reported function, and fear of falling.

Conclusion

Relatively young PLHIV present with biomechanical gait and balance impairments that resemble patterns noted in elders, especially under dual task conditions. The 5STS test is recommended as a valid clinical screening test. These findings improve understanding of movement impairments in PLHIV and highlight the need for early screening. Further research is needed to determine whether the 5STS test predicts falls, and whether the impairments noted in PLHIV are reversible. Early identification and rehabilitation can reduce healthcare utilisation needs in PLHIV.

OPSOMMING

Agtergrond

MIV-1 infeksie het ontaard in ‘n kroniese toestand. Alhoewel persone wat leef met MIV-1 infeksie (PLMIV) nou ‘n bykans normale lewensverwagting het, is loopverwante aantastings steeds kommerwekkend aangesien dit vroeg voorkom en kan lei tot valverwante beserings. Tans heers ‘n swak begrip van hoe bewegingspatrone aangetas word, weens ‘n tekort aan biomeganiese studies. Drie-dimensionele (3D) bewegingsanalise kan insig verleen aangaande beweginspatrone en bydra tot die identifisering van ‘n geldige verrigtings-gebaseerde siftingstoets vir die waarneming van vroeë bewegingsaantastings in PLMIV.

Doel

Die doel van hierdie navorsing was om looppatroon- en balansaantastings in PLMIV te ondersoek deur middel van 3D-bewegingsanalise. ‘n Verdere doelwit was om die 3D-analise bevindinge (via ‘n looppatroon opsommings-telling), selfvermelde funksie, asook geskiedenis van en vrees vir neerval te korreleer met fisiese verrigtings-toetse wat in kliniese pratkyk oorweeg mag word om te sif vir vroeë funksionele agteruitgang in PLMIV.

Metodes

Die studie het drie dele behels:

Deel I het ‘n sistematiese oorsig behels wat objektiewe looppatroon- en balansaantastings in PLMIV beskryf. Resultate het bygedra tot die teoretiese grondwerk vir die studie se konsepsualisering en ook tot die keuse van klinies-relevante biomeganiese uitkomste en verrigtingsgebaseerde toetse.

Deel II het bestaan uit geldigheids- en betroubaarheids-toetsing van ‘n 3D-loopanalise (3DLA) stelsel, nuut aangeskaf deur die bewegingslaboratorium, in 16 gesonde studente vrywilligers asook in agt opeenvolgend-vervorwe PLMIV en agt gemeenskaps-ooreenstemmende seronegatiewe deelnemers (SND). Die studies het die geldigheid en betroubaarheid van spesifieke 3DLA uitkomste bepaal om gepaste data interpretasie in die volgende fase moontlik te maak.

Deel III het die hoof waarnemingstudie behels wat ‘n dwarssneebeskrywing verskaf het van die kern biomeganiese kenmerke in 50 PLMIV vergeleke met 50 gemeenskap-ooreenstemmende SND (opeenvolgende steekproefneming). Die studie is uitgevoer in ‘n

kliniese omgewing en verrigtingsgebaseerde toetse is geëvalueer bykomstig tot die 3D-bewegingsanalise. Resultate van die looppatroonanalise, valverwante uitkomste en selfvermelde funksie is gekorreleer met die kliniese toetsverrigting om die mees geldige verrigtingsgebaseerde siftingstoets te bepaal.

Hoofresultate

Die sistematiese oorsig (Deel I) het ‘n mate van konsensus bevind dat PLMIV stadiger loop en ‘n verhoogde middelpunt van drukking (MVD) omvang van beweging (OVB) het, asook posturale reflekslatentheid, veral onder uitdagende toestande. Geen ingeslote studies het gebruik gemaak van 3DLA nie. Die geldigheid- en betroubaarheid-studies (Deel II) het demonstreer dat, met gereelde herkalibrering, die 3DLA stelsel looppatroon-biomeganika betroubaar meet in SND en PLMIV, met die uitsondering van vier diskrete gewrigshoeke. Die stelsel/model is hoogs vergelykbaar met die verwysingstelsel na die inagneming van die verskille in die biomeganiese model. Die veldwerkstudie (Deel III) het getoon dat die looppatroon van PLMIV (mediaan-ouderdom: 36.61 jaar) beduidend stadiger en oormatig rigied was vergeleke met SND (mediaan-ouderdom: 31.10 jaar). Hierdie patroon het manifesteer tydens ‘n selfgekose loopspoed of tydens die uitvoer van ‘n dubbele taak. Dubbeltaak-loop het verder veranderinge getoon in heup- en kniegewrigs OVB in ‘n distaal-tot-proksimale patroon-aanpassing. PLMIV het ook verhoogde MVD OVB getoon tydens dubbeltaak-eenbeenstaan. PLMIV was beduidend stadiger om die Vyfmaal Sit-Tot-Staan (5STS) Toets te voltooi. Stadiger sit-tot-staan het ‘n beduidende verwantskap getoon met ‘n meer rigiede looppatroon, laer vlakke van selfvermelde funksie en ‘n vrees vir val.

Gevolgtrekking

Relatiewe jong PLMIV toon verskeie aantastings van looppatroon- en balansbiomeganika wat tot ‘n mate ooreenstem met patrone wat gewoonlik in ouer volwassenes waargeneem word, veral tydens die uitvoer van ‘n dubbele taak. Die 5STS-toets word aanbeveel as ‘n geldige siftingstoets. Hierdie bevindinge verbeter die begrip van bewegingsaantastings in PLMIV en beklemtoon die belang van vroeë siftingstoetsing. Verdere navorsing word benodig om te bepaal of die 5STS-toets val-insidente kan voorspel, en of die aantastings in PLMIV omkeerbaar is. Vroeë identifisering en rehabilitasie kan die behoeftes aan gesondheidsorg onder PLMIV verminder.

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LIST OF ABBREVIATIONS

3DGA	Three-dimensional gait analysis
30sSTS	Thirty-Second Sit-To-Stand
5STS	Five-Times Sit-To-Stand
6MWD	Six-Minute Walk Distance
6mWT	Six-metre Walk Test
AIDS	Acquired Immune Deficiency Syndrome
ANOVA	Analysis of variance
ANCOVA	Analysis of covariance
AP	Anteroposterior
ART	Antiretroviral therapy
ASIS	Anterior superior iliac spine
BMD	Bone mineral density
BMI	Body mass index
BQI	Bone quality index
cART	Combination antiretroviral therapy
CDC	Centre for Disease Control
CHC	Community Health Centre
CGM	Conventional Gait Model
CI	Confidence interval
CL	Confidence limit
CNS	Central nervous system
COG	Centre of gravity
COM	Centre of mass
COP	Centre of pressure
DT	Dual task
EC	Eyes closed
EGVI	Enhanced Gait Variability Index

EO	Eyes open
EQ-5D-5L	European Quality of Life Five-Dimension Five-Level questionnaire
FA	Feet adjacent
GC	Gait cycle
HAART	Highly active antiretroviral therapy
HHD	Hand-held dynamometry/hand-held dynamometer
HIV-1	Human Immunodeficiency Virus Type 1
HR	Heel rise
HREC	Health Research Ethics Committee
HRQOL	Health-related quality of life
IC	Initial contact
IMC	Inertial motion capture
IMU	Inertial measurement unit
ISB	International Society of Biomechanics
LL	Long loop
LoA	Limits of agreement
LOS	Limits of stability
MAD	Mean absolute difference
MCID	Minimum clinically important difference
MeSH	Medical Subject Heading
ML	Mediolateral
MOS-HIV	Medical Outcomes Study HIV Health Survey
MR3	myoRESEARCH 3 software
MSt	Mid-stance
n	Number of participants
NA	Not applicable
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitors

OIC	Opposite initial contact
OMC	Optical motion capture
OTO	Opposite toe-off
PI	Protease Inhibitor
PiG	Plug-in-Gait
PLHIV	People living with HIV-1 infection
PPB	Health ABC Physical Performance Battery
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSIS	Posterior superior iliac spine
QUS	Quantitative ultrasound
RMSE	Root-mean-square error
ROM	Range of motion
SD	Standard deviation
SEM	Standard error of measurement
SL	Short loop
SLS	Single leg stance
SNP	HIV-1 seronegative participants
SOS	Speed of sound
SOT	Sensory Organisation Test
SPPB	Short Physical Performance Battery
STA	Soft tissue artefact
STS	Sit-To-Stand
SU	Stellenbosch University
TO	Toe-off
TSPs	Temporal, spatial, temporophasic and temporospatial parameters
TSt	Terminal stance
TV	Tibia vertical

CHAPTER 1
INTRODUCTION

1.1. Background

HIV-1 infection has evolved into a manageable chronic condition due to the success of highly-active antiretroviral therapy (HAART).[1] Despite the fact that people living with HIV-1 infection (PLHIV) treated with HAART now have a near-normal life expectancy, age-related comorbidities and declines in physical function remain of concern as they occur relatively early.[2,3] HIV/AIDS was the 33rd most important cause of disability-adjusted life years (DALYs) globally in 1990, but increased steeply to fifth position in 2010.[4] In Sub-Saharan Africa, including South Africa, a high prevalence of HIV-associated disability, including impairments in mobility and motor function, is reported.[5–7] The prevalence of HIV-1 infection is most prominent and rising amongst working-aged (20 to 60 year-old) adults in South Africa.[8] The younger Sub-Saharan population living with HIV-1 infection implies that costly, long-term morbidity management will be needed in PLHIV.

1.1.1. Motor impairments related to HIV-1 infection: Early origins

June 5, 1981, marks the first official reporting of what was to become one of the most devastating and widespread infectious pandemics to have emerged in recent history.[9] A retrovirus, now termed human immunodeficiency virus type 1 (HIV-1), was subsequently confirmed as the principal aetiological agent and in September 1982 the US Centres for Disease Control and Prevention (CDC) coins the term “AIDS” (Acquired Immune Deficiency Syndrome) for the first time. Ever since this first definition of AIDS, motor function impairments, often along with cognitive dysfunction, were noted and described as defining characteristics of HIV/AIDS.[10,11] Psychomotor slowing (for example slowed motor and verbal responses; potentially progressing to an akinetic state) was described as the most common prodromal presentation of AIDS, along with impaired memory and concentration.[10,12] At that time, it was estimated that about half of PLHIV had a motor or cognitive impairment, or both.[10] Functional capacity in PLHIV was severely reduced by psychomotor impairments – which were described as being progressive in nature. Signs and symptoms became severe in the late stages of the disease. These impairments were thought to indicate direct brain infection by the AIDS-causing retrovirus.[10]

Two landmark papers[10,12] initially described the early motor impairments observed in AIDS. These researchers indicated that during the asymptomatic stages of HIV-1 infection, motor signs were already present, albeit less apparent. The initial signs of motor impairment that were observed included tremor, slowing of alternating movements of the extremities and loss of rapid and fine motor function of the fingers. During these early stages of the syndrome, gross motor functional ability was also affected, since gait was typically slower and mildly unsteady, with rapid turns being performed with less control and confidence. As the syndrome progressed into the later stages, walking difficulties became more notable and included gross weakness and general hypokinesia.[10] In severe cases, gait slowness and instability necessitated use of a walking aid to prevent falling. Gait problems were exaggerated by ataxia, leg weakness, abnormal reflexes and tremors.[10] These significant impairments, particularly in association with cognitive impairments, were indications for aggressive antiretroviral chemotherapy to reduce symptoms and enhance function.[12]

1.1.2. Motor impairments related to HIV-1 infection: The antiretroviral (ARV) treatment era

Advances in the treatment of opportunistic infections were observed following the advent of antiretroviral (ARV) therapy in 1987.[13] As a result, the lifespan of PLHIV improved significantly.[14,15] Despite an improvement in the severity of many of the HIV-defining motor impairments which were initially observed, the incidence and prevalence of ARV side effects such as sensory distal peripheral neuropathies increased.[16] These effects were arguably due to the neurotoxic effects of specific ARV drugs such as stavudine.[17–19] Although largely phased out, as recommended by the World Health Organisation (WHO), a substantial proportion of South African PLHIV are currently still prescribed stavudine due to lack of a cost-effective alternative.[19,20] The most common signs and symptoms of peripheral neuropathies among South African PLHIV include pain of the feet or just proximal to the feet, numbness and paraesthesia, absent ankle reflex and reduced vibration sense.[19] The presence of such symptoms significantly reduces quality of life and function.[19,21] Since peripheral neuropathies primarily affect the lower limbs and feet, it often impairs balance control and subsequently functional walking performance.[22]

1.1.3. Motor impairments related to HIV-1 infection: The highly-active antiretroviral therapy (HAART) era

Twenty-two years ago, in 1996, early forms of combination antiretroviral therapy (cART) were introduced,[23] leading in the current treatment era of HAART. HAART entails the use of combination ART, typically comprising three or more drugs, aimed at reducing plasma virus levels below limits of detection.[24] Modern HAART regimens have less neurotoxic effects than older versions, and thus there is a lower risk of developing peripheral neuropathy.[25] However, the prevalence of peripheral neuropathy remains quite high among PLHIV (between 30% and 62%), and the prevalence of locomotor impairments remains a concern[26–29] – regardless of the presence of peripheral neuropathy.[30] In a Cape Town-based study by Joska et al.,[26] participants with severe neurocognitive impairment (indicated by a high global deficit score [GDS] achieved in a neurocognitive test battery) at the commencement of HAARTillustrated significant improvement (indicated by a lowered GDS) within a one-year treatment period. However, mild-to-moderate neuro-motor impairments were still noted in one-quarter of the sample; particularly in domains associated with deep grey nuclei[31] such as psychomotor processing and learning. Thus, the prevalence of neuro-motor impairments remains a concern despite HAART. Persistent neuro-inflammation of the central nervous system (CNS) has been hypothesised as a major explanatory phenomenon – especially of frontal and subcortical grey areas which indirectly contribute to locomotion and balance[26,31] and perhaps more so than impairment of the peripheral nervous system.[32] In addition, HAART may also impose direct drug toxicity.[25] Individuals with persistent neurocognitive effects may therefore continue to demonstrate fine as well as gross motor impairments.[33]

1.1.4. Evolution of HIV-1 infection into a chronic condition

Over the past 30 years, significant improvements have been made in the management of HIV-1 with drug-related therapies to reduce infections. Due to powerful HAART suppressing viral replication, HIV has now evolved into a long-term chronic disease. Furthermore, in Sub-Saharan Africa specifically, PLHIV are relatively younger compared to developed countries, are usually engaged in full-time employment and have domestic, family and social responsibilities. Symptoms such as pain and poor functional ability have a profound negative effect on health, work productivity and healthcare utilisation.[34] These younger Sub-Saharan and South African populations will likely live well into older age with HIV-1 infection, with the implication that the management of morbidity will be needed at an earlier age and for a longer period. This underscores the need for clinicians and researchers alike to reprioritise

investigations into understanding the impact of this chronic condition on the individual's quality of life. Indeed, optimisation of quality of life is now a priority goal as part of the comprehensive care for PLHIV.[25] From an ethical point of view, extending the lifespan of individuals without sufficient efforts to significantly enhance quality of life accordingly, cannot be justified. Improved management of functional problems related to HIV-1 infection to enhance quality of life is thus warranted.[6]

1.1.5. In summary

This background illustrates the plausible advances in HIV-1 management, paralleled by challenges related to morbidity and its consequences for PLHIV residing in Sub-Saharan Africa. It illustrates that efforts to enhance quality of life and function in PLHIV is a pressing concern. Despite the extraordinary success of HAART in extending the lives of PLHIV and reducing many morbidities, motor impairments remain prevalent. Adding years to life without substantial concurrent efforts to maximise quality of life for these added life years cannot be ethically justified. This behoves scientific investigations to understand the interplay of neuromotor impairments and functional trajectories towards disability in PLHIV. Such investigations can make a meaningful humanistic contribution towards the lives of PLHIV, particularly those living in Sub-Saharan Africa. In addition, addressing morbidity can ultimately yield substantial economic gains due to reduced healthcare utilisation and improved adherence to HAART, which is a secondary effect to improved quality of life.[35]

1.2. Research motivation

South Africa has the highest prevalence of HIV-1 infection in the world, with an estimated 7,52 million PLHIV in 2018, meaning that about one in every eight South Africans is HIV-1 seropostitive.[36] These alarming statistics, along with the fact that HIV-1 now manifests as a chronic condition, highlight the substantial burden of HIV-1 on the population's well-being and the healthcare system.

In the context of South Africa, reduced physical functional performance may be prevalent in PLHIV. This may be because some individuals have limited access to ART or present late for treatment due to the stigma of the disease or cultural issues. No or delayed treatment leads to earlier progression of the disease into advanced stages. In these advanced stages, declines in function is marked.[37,38] South African PLHIV may also be subjected to earlier functional decline as neurocognitive dysfunction is often reported in relatively young individuals (mean ages ranging from 29.75 to 38.50 years in a systematic review[39]), which is often associated

with depression, mobility problems and activity limitations[39,40] The onset and rate of functional decline is thus of concern among South African PLHIV.

Due to the many and complex effects that the virus itself or its treatment can have on the body, everyday functioning of PLHIV may be severely affected by HIV-1 infection.[37,41] South African PLHIV receiving HAART have been reported to experience a mean of ten HIV-associated symptoms.[42,43] These commonly include psychological and physical symptoms[i] such as "feeling sad", sleep disturbances, weight maintenance (unwanted weight loss), numbness or tingling of the hands and feet, pain, and muscle weakness.[37,42] Subsequently, activity levels are often affected, especially in the domains of mobility, domestic life, self-care and ability to work[44,45] and quality of life (including the ability to function) is noticeably reduced.[43,46] Of further concern is that PLHIV with more self-reported symptoms are less adherent to HAART.[35] The number of symptoms experienced is also associated with substance abuse and psychiatric illness.[47] There are indications that symptom management improves quality of life and even virologic suppression.[48] Understanding of HIV related symptoms which impact on functional performance is crucial to improve the quality of life.

Many functional activities are dependent on the integrity of lower limb neuromusculoskeletal structures[49] and lower limb function is predictive of future disability.[49,50] PLHIV in high-, as well as in lower-middle income countries, have shown to have some form of lower limb impairment, despite controlled viral load.[2,38,51] Despite effective viral suppression, PLHIV also experience non-AIDS-defining complications, resembling geriatric processes.[52,53] This hypothesised accelerated or accentuated ageing may manifest in middle-aged PLHIV as low muscle mass, low bone mineral density (BMD) and low insulin-like growth hormone (IGF-1) and IGF-1 binding protein 3.[54] Low BMD, in addition to muscle weakness, is associated with balance problems and increased fall risk.[2,55] People with reduced functional performance are less likely to participate in regular physical activities, amplifying the decrease in BMD and muscle strength.[54] The compounded effect of these factors may explain the fourfold increased risk for hip fractures in PLHIV relative to seronegative individuals.[56] These problems face relatively young South African PLHIV compared to their seronegative peers.[57] Functional decline and its consequences (such as falls) increases morbidity in people with HIV/AIDS as well as their healthcare needs or utilisation.

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[i] *Symptoms defined using either the Memorial Symptom Assessment Scale-Short Form (MSAS-SF) or International Classification of Functioning, Disability and Health (ICF) checklist. Data from cross-sectional self-report studies.*[37,42,43]

Functional performance related to impaired walking ability is a particular concern in PLHIV.[2,32,51,58,59] It has been reported that a quarter of PLHIV have a reduced six-minute walking distance.[2] Peripheral neuropathies related to ARVs can lead to decreased walking ability and speed[22,32] and reduced balance is also evident independent of such neuropathies.[30] In addition to walking problems, about half of PLHIV also have difficulty in performing other functional movements such as rising from a chair.[2] Successful and safe occupational, societal and domestic functions may thus be threatened in PLHIV.

1.2.1. The knowledge gap

It is clear that the motor system is affected in PLHIV; yet a poor understanding of exactly why and how it is altered remains; and several gaps exist in the literature. In Sub-Saharan Africa, published literature about functional performance is limited to subjective self-reports such as "difficulty walking".[7,37,38,45] The international literature also primarily reports on temporal information such as how long it takes to perform a specific clinical functional test (e.g. duration of a four-metre walk).[2,30,59,60] Despite the recommendation to standardise clinical tests in PLHIV in order to provide comparable objective information, clinical tests such as a timed gait test in isolation remain mere proxy measures and do not allow the identification of the specific, perhaps subtle, underlying movement impairments or quality of a gait pattern. Instrumented motion analysis may allow greater sensitivity and precision in the description of motor impairments in PLHIV; potentially unveiling currently undocumented changes in movement quality. Unfortunately, there is also a dearth of research published on quantitative biomechanical analyses of walking gait in PLHIV. Using sophisticated 3D-movement analytical techniques, instrumented analyses can improve understanding of contributors to functional decline by unlocking underlying scientific contributors. Three-dimensional gait analysis (3DGA) is one of the few measurement approaches allowing quantification of the dynamic implications of relevant impairments during a functional activity such as gait.[61] Such quantitative information may assist in identifying the most valid clinical screening tests for detecting early functional decline, to prevent consequences such as falls. In addition, it can inform the design of effective interventions by directing rehabilitation protocols towards key deficits.

1.3. Overall aim of the dissertation

The overarching aim of this dissertation was to provide novel quantitative information about the locomotor impairments found among PLHIV residing in the Cape Winelands District of the Western Cape, South Africa, using state-of-the-art 3DGA technology. It further aimed to

correlate the findings of 3DGA (via a quantitative summary score of gait), as well as self-reported function and history and fear of falling, to selected physical performance tests which may be considered in clinical practice to screen for early functional decline in PLHIV.

1.4. Significance of the research

Using state-of-the-art technology in a clinically relevant context, this novel project provides new scientific information about the locomotor impairments of PLHIV relative to SNP. It is also the first project aimed at correlating clinical performance-based tests to quantitative 3DGA, self-perceived functional ability and history and fear of falls in PLHIV. The comprehensive dataset allowed for the identification of the most valid clinical test which may be used in clinical practice to screen for functional decline in PLHIV. Early identification of functional decline will reduce morbidity and healthcare utilisation among South African PLHIV. Improved functional ability is also positively associated with treatment adherence in people affected by this prevalent syndrome.

1.5. Research questions

The primary research question was two-fold:

i. Are there differences in walking gait biomechanics and in static postural stability in PLHIV compared to HIV-seronegative participants (SNP)?
ii. Which clinical test correlates best with a quantitative 3D-analysis of gait, subjective self-perception of functional ability and/or history and fear of falls in PLHIV?

As groundwork towards answering the primary questions, the following research question was also assessed:

i. Is the concurrent validity, as compared to the current reference standard, and within-session reliability of 3DGA outcomes measured by a frequently recalibrated inertial motion capture (IMC) system clinically acceptable in healthy adults, and can these results be assumed in a community sample including PLHIV?

1.6. Methodology overview

The project was divided into three parts, comprising of a theoretical background and three distinct but related primary observational studies. **Part I** involved a literature review and a

systematic review and meta-analysis. The systematic review established and synthesised the current available evidence regarding objective impairments of gait and balance in PLHIV. **Part II** involved laboratory-based primary research and consisted of two observational concurrent validity and within-session reliability studies. These were aimed at ascertaining the reliability and concurrent validity of gait analysis outcomes using a newly-acquired portable IMC system in healthy volunteers (Study One, Chapters 4 and 5) and in a community sample of PLHIV and SNP (Study Two, Chapters 4 and 6). **Part III** comprised of an observational cross-sectional design with an analytical component. The IMC system was implemented in a clinical setting to measure the 3D gait biomechanics of 50 PLHIV and 50 SNP from the same community. A pressure mat captured quantitative balance (postural stability) data. Clinical functional test performance was also recorded, along with collecting data on self-reported function and retrospective fall-history. These data were correlated to establish the validity of the clinical test as compared to a quantitative 3DGA, and ascertain its ability to screen for self-reported functional problems and/or fall risk.

1.7. Structure of the dissertation

According to the three-phased study methodology, the dissertation is divided into three parts (Chapters 2 to 8). Figure 1.1 provides a schematic overview of how the research process is presented in the dissertation. The three Parts are preceded by this general introduction (Chapter 1) and followed by the comprehensive discussion chapter (Chapter 9), study limitations (Chapter 10) and recommendations (Chapter 11). The dissertation briefly concludes with Chapter 12 (the Conclusion).

1.7.1. Part I: Theoretical groundwork

Part I of the dissertation introduces the reader to HIV-1 infection, its current manifestation as a chronic condition and the neuromusculoskeletal consequences posing some unique challenges to patients and rehabilitation therapists alike. To this effect, Chapter 2 is presented as a traditional literature review, and explores concepts underlying the current research, including an hypothesis of accelerated or accentuated ageing in chronic HIV-1 infection. In Chapter 3, the current knowledge gap regarding objective and quantitative movement impairments in PLHIV is systematically explored by means of a published systematic review and meta-analysis of observational studies.[62] The chapter presents the methodological procedures and results of the systematic review, as well as a discussion of the implications of the findings for research to follow. The outcome of Part I is a clarification of how HIV-related locomotor impairments may be understood within a framework of accelerated or accentuated

ageing. These reviews also informed the definition of clinically relevant gait outcomes (commonly observed in elderly gait) for clinometric assessment in Part II, and in-field use in Part III.

1.7.2. Part II: Determining the validity and reliability of a newly-acquired portable 3D motion analysis system for in-field use

Part II of the dissertation presents the validation of a portable 3DGA system, newly acquired by the Stellenbosch University (SU) Central Analytical Facilities (CAF) 3D Human Biomechanics Unit, versus the current reference standard. The specific methodology underlining the two interlinked observational laboratory-based primary studies is contained in Chapter 4, while the results of the studies in healthy volunteers and a community sample are presented separately in Chapters 5 and 6, respectively. Part II resulted in determining (1) the validity and reliability of 3DGA outcomes and (2) the measurement error of the IMC system, to aid appropriate interpretation in the cross-sectional field study.

1.7.3. Part III: In-field biomechanical analysis of gait and balance in people living with HIV-1 infection (PLHIV) relative to HIV-seronegative participants (SNP)

Part III of the dissertation presents the main cross-sectional primary study and incorporates the theoretical hypotheses derived from Part I along with the technical insights gained from Part II. Part III reports the procedures and outcomes of the in-field use of the IMC system to cross-sectionally describe clinically relevant motion analysis outcomes in PLHIV relative to community-matched SNP. An analytical component was included to correlate 3D-analysis results, fall-related outcomes and self-reported function to clinical test performance. Chapter 7 presents the study methodology while Chapter 8 presents the results of the comparisons and correlations. The outcome of Part III was the description of key biomechanical characteristics of gait in PLHIV. A quantitative dataset was established, which assisted in determining the most valid clinical screening test which may be used to detect early motor impairments in PLHIV.

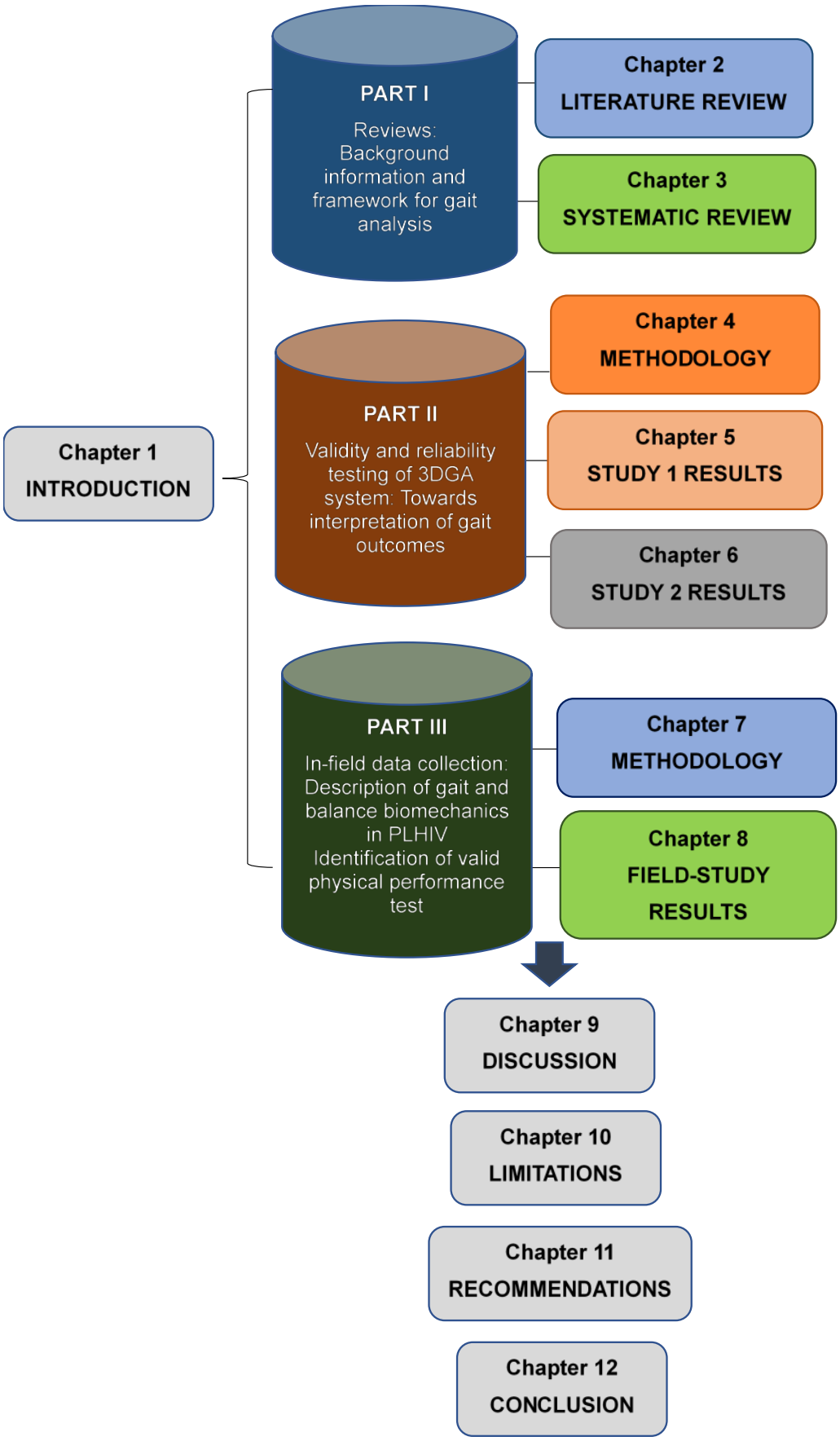

Figure 1.1. Schematic representation of the dissertation structure.

PART I

CHAPTER 2
LITERATURE REVIEW

2.1. Introduction

HIV-1 infection remains incurable, but has evolved from an acute and rapidly fatal disease into a manageable chronic condition. This has mostly been due to the success of introducing highly active antiretroviral therapy (HAART). Modern-day regimens are powerful and mostly well-tolerated. However, despite the fact that HAART can rapidly suppress HIV blood concentrations to being undectable[13] it does not fully restore health.[63] Thus, along with HIV-1 becoming a chronic disease, much of HIV research has shifted its focus to the increasing rate, and consequences, of non-AIDS morbidity – which has also been termed "early ageing".[54,64,65]

The following literature review is the first of two chapters constituting Part I of the dissertation (Figure 2.1). This chapter presents an overview of the literature regarding chronic HIV-1 infection, including the causes and consequences of HIV-related motor impairments. HIV-1 is introduced by means of briefly reviewing its natural history and HAART pharmacotherapy, where after the effects of chronic HIV-1 infection, its associated comorbidities and HAART on bodily systems is described. The question of an accelerated or accentuated ageing phenotype is raised, and fall risk amongst PLHIV is reviewed. Next, the reader is introduced to the conceptualisation of HIV-1 into a framework of rehabilitation, along with a working definition of "function" as used in this dissertation. The assessment of lower limb impairments and function, including instrumented (quantitative) assessment, and its proposed utility in PLHIV is briefly reviewed. The chapter concludes with a description of gait and balance patterns indicative of advancing age or fall risk in the general population, which served to inform the selection of analysis outcomes in PLHIV.

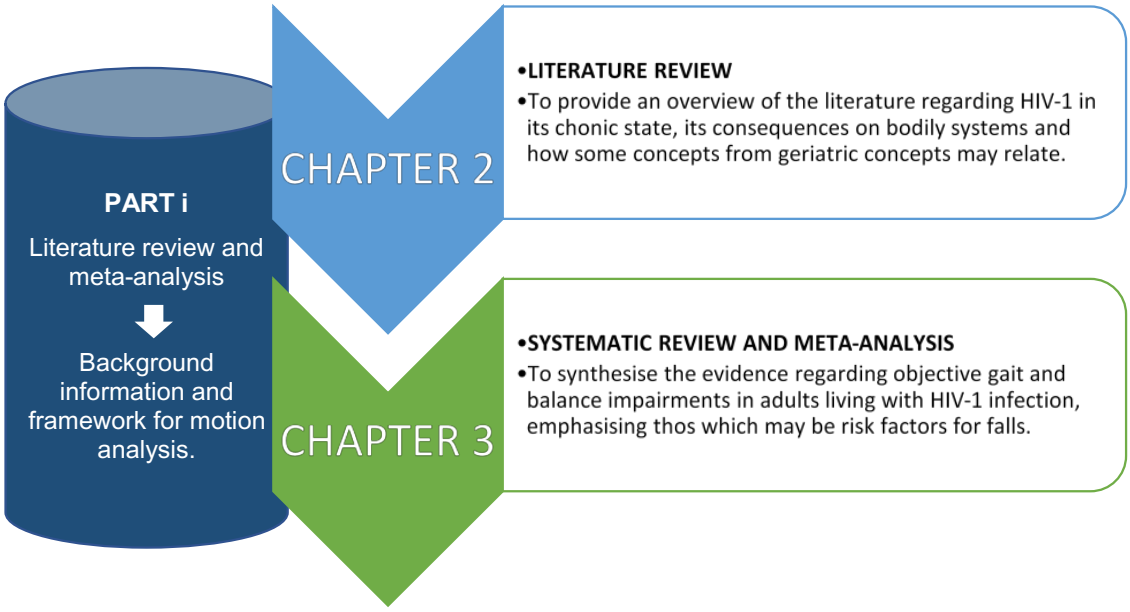

Figure 2.1. Schematic layout of the structure of Part I of the dissertation.

2.2. Introduction to HIV-1

2.2.1. Prevalence

Home to only 12% of the global population, Sub-Saharan Africa accounts for 71% of the enormous worldwide pandemic of HIV-1 infection.[66] Nearly one in every eight South Africans (13.10%) is living with HIV infection[36]; the total estimated adult prevalence (ages 15 to 49 years) being 19% in 2018.[36] South African women aged 30 to 34 and men aged 35 to 39 account for the majority of the adult prevalence.[67] Although working-aged PLHIV still bear the brunt of the burden in South Africa, closer inspection of the trends in prevalence suggests an ageing HIV-population much like trends in high-income countries. Despite a 44% reduction[ii] the rate of new HIV infections over the past five years,[68] the total number of South Africans living with HIV-1 infection has increased from about 4,25 million in 2002 to 7,52 million by 2018.[36] Prevalence among young South Africans (15 to 24 age bracket) has decreased from 6.7% in 2002 to 5.5% in 2018.[36] The ageing of the HIV epidemic in Sub-Saharan Africa has

[ii] *Along with HAART scale-up, universal test-and-treat initiatives aimed at realising the Sustainable Development Goal of ending the AIDS epidemic by 2030 contributed to these statistics[516] – such as the UNAIDS-endorsed 90-90-90 target (also included in South Africa's National Strategic Plan for HIV, TB and STIs 2017 – 2022).*

not been as extensive as in high-income countries: 14.3% of PLHIV in Sub-Saharan Africa are currently aged over 50 years[69] (versus about 50% in the USA).[70] Yet, trends are expected to follow suit and South African statistics are projected to triple within the next couple of decades.[71]

Unfortunately, there has also been a large global and local increase in the burden caused by HIV. The Global Burden of Disease Study 2015[72] alarmingly showed that in 1990, HIV-1 infection was the 33rd highest ranking cause of disability-adjusted life years (DALYs) globally, but that it has increased steeply to tenth position in 2015. Regarding South Africa, in 2015, HIV-1 infection was the top nonfatal cause of health loss.[73]

2.2.2. Natural history

Genetically, HIV Type 1 (HIV-1; globally the most prevalent and pathogenic of the two types of HI virus) belongs to the genus *Lentivirus,* of the family *Retroviridae*.[74] Lentiviruses cause persistent infections, with an extended clinical latency period, ongoing viral replication and central nervous system (CNS) involvement.[74] The virus resides in bodily fluids and is transmitted either during sexual contact across mucous membranes, by mother-to-child exposure, or by needlestick injury.[75] HIV-1 RNA (viral load; undetectable when falling below 50 HIV-1 RNA copies/mL) and CD4+ T lymphocyte (CD4+) cell count (normally ranging between 500 and 1400 cells/μL) are surrogate HIV disease markers.[76] Following infection, HIV initially binds to target CD4+ cells where after it is transported to regional lymph nodes.[13] Along with incipient and rapidly progressing viral replication, ongoing and productive infection commences. CD4+ cells are rapidly (and possibly permanently) destroyed. Additionally, penetration of microbial translocation products into the systemic circulation occurs as the gut mucosa ruptures.[13] At the same time all body compartments, including the CNS, become infected.

Primary HIV-1 infection is often overlooked due to the non-specific symptoms.[13] Early diagnosis is however important; for the patient and the larger community, as the viral load is usually high, with a high risk of transmitting the disease. After this so-called acute HIV syndrome, a chronic, asymptomatic phase of clinical latency is entered, which may last for decades if viral load is effectively suppressed by HAART.[75] Usually, symptomatic disease only develops when CD4+ count declines to below 350 cells/μL, at which stage AIDS-associated events such as tumors or opportunistic infections start to occur.[13] If left untreated, AIDS is inevitably fatal.

2.2.3. Highly active antiretroviral therapy (HAART)

Antiretroviral drugs (ARVs) were introduced in South Africa in 1996; however, the national roll-out of HAART (combining multiple ARVs that act on different viral targets) only officially began in 2003. By June 2017, globally, 20.9 million PLHIV were using HAART.[77] Today South Africa has the world's largest Government-sponsored HAART rollout programme and currently 56% of South African PLHIV are receiving HAART.[78]

HAART entails the use of combination ARV treatment, typically comprising three or more drugs, with the main aims of reducing plasma virus levels below detectable limits, restoring immune function, reducing opportunistic infections, enhancing quality of life, and reducing the community impact of HIV transmission.[24] The health benefits of early HAART initiation are increasingly recognised. Since 2016, South African guidelines, in accordance with those of the World Health Organisation (WHO), recommend immediate HAART-initiation following HIV diagnosis, regardless of CD4+ count.[79] If taken as directed, HAART effectively suppresses viraemia by acting directly on the HI virus and impairing viral multiplication (i.e. by blocking, at different points in the virus' life cycle, the action of enzymes used by the virus to replicate itself within CD4+ cells). Viral destruction of CD4+ T-cells is thus mitigated, allowing functional reconstitution of the immune system.[80] However, the virus is not eradicated and re-emerges in almost all cases when HAART is ceased (due to persistent infected cell reservoirs despite the absence of viruses in the blood)[81] which highlights the importance of adequate adherence.

Antiretroviral agents are categorised into various classes according to their molecular mechanism and resistance profiles.[82] Table 2.1 summarises the classes of HAART currently available in South Africa, along with their main mechanism of action.

Table 2.1. Summary of the classes of HAART available in South Africa.

Generic name	Class	Mechanism of action	Specific action
Tenofovir (TDF)	NtRTI	Reverse transcriptase inhibition	Nucleic acid analogues mimic normal DNA building blocks, inhibiting viral RNA transcription to DNA.
Lamivudine (3TC)	NRTI		
Emtricitabine (FTC)			
Abacavir (ABC)			
Zidovudine (AZT)			
Stavudine (d4T)			
Didanosine (ddI)			

Efavirenz (EFV)	NNRTI		Inhibits final maturation stages of HIV replication, resulting in non-infective viral particles.
Nevirapine (NVP)			
Rilpivirine (RPV)			
Etravirine (ETR)			
Atazanavir (ATV)	PI	Protease inhibition	Inhibits the final maturation stages of HIV replication, resulting in non-infective viral particles forming.
Darunavir (DRV)			
Saquinavir (SQV) (rarely used)			
Lopinavir/ritonavir (LPV/r)	Boosted PI		
Raltegravir (RAL)	InSTI	Inhibition of viral integration	Prevents transfer of proviral DNA strands into host chromosomal DNA.
Dolutegravir (DTG)			
Maraviroc (MVC)	CCR5 blocker	Entry inhibition	Binds to viral gp41, gp120, host cell CD4+ or chemokine (CCR5) receptors.

Abbreviations: CCR5 = C-C chemokine receptor type 5; InSTI = integrase inhibitor (integrase strand transfer inhibitor); NNRTI = non-nucleoside reverse transcriptase inhibitors; NRTI = nucleoside reverse transcriptase inhibitor; NtRTI = nucleotide reverse transcriptase inhibitors; PI = protease inhibitor.

The chronicity of HIV-1 implies that more PLHIV are being placed on HAART and will remain on these drugs for longer (as HAART is required for the rest of a person's life).[83] Unfortunately, HAART usually involves a rather complex medication regimen and is often associated with adverse reactions.[84] Short-term adverse reactions such as pain, fatigue and gastro-intestinal effects potentially threaten successful HAART initiation and maintenance.[84] Long-term toxicity is still an emerging area of research, but often includes mitochondrial toxicity (which could lead to myopathies, neuropathy, pancreatitis, lactic acidosis, hepatic steatosis, and lipodystrophy),[84,85] pain and hypersensitivity, bone mineral density (BMD) deficits and more[83,86] (see also the next sections of this review). Specific adverse effects vary between drugs, drug classes, and patients. Nucleoside reverse transcriptase inhibitors (NRTIs), for example, may theoretically also inhibit non-viral enzymes involved in DNA formation, including human DNA polymerase γ, with subsequent disruption of mitochondrial function.[84] In addition, overlapping and additive toxicities due to concomitant medication use, comorbidities that exacerbate adverse effects, drug-drug interactions and genetic factors that predispose patients to specific reactions may all add to the risk and impact of adverse effects.[84] Such

morbid effects negatively affect adherence, which can lead to drug resistance and treatment failure - and thus even further morbidity and mortality.[87]

2.3. Effects of chronic HIV-1 and HAART on the human body

HIV-1 can persist in HAART-treated PLHIV because of latent infection of long-lived cellular reservoirs (resting memory CD4+ cells), immune dysfunction, persistent residual viral replication in lymphoid tissues (in some individuals), and anatomical reservoirs (mainly the CNS).[88] Chronic HIV infection is typically accompanied by other comorbid non-communicable diseases. Until fairly recently, the high mortality rates caused by AIDS have mostly masked the emerging burden of non-communicable diseases associated with HIV-infection; which adds substantially[89] to the transitioning and quadruple disease burden in SA.[89] The following sections review the various effects of chronic HIV-1 infection as well as HAART on the body.

2.3.1. Chronic inflammation and immune activation

Despite viral suppression, HIV-1 infection is associated with persistent immune activation (involving the innate, adaptive and intrinsic immune systems), inflammation and abnormalities in coagulation; all of which increases morbidity and mortality.[90,91] This residual and abnormally regulated inflammatory state is thought to be driven primarily by toll-like receptor activation, telomere shortening, continuing low-level viraemia, gut epithelial damage and microbial translocation, as well as co-infections (such as the cytomegalovirus or hepatitis C virus). In addition, multimorbidity, substance use and lifestyle factors (such as physical inactivity and diet) also adds to chronic inflammation and immune activation.[91,92]

2.3.1.1. Functional ramifications of chronic inflammation and immune activation

Evidence is building that persistent inflammation and immune activation is associated with the increasing occurrence of non-AIDS morbidity, including physical functional ramifications.[93,94] The first study[93] to compare immune activation, immunosenescence and microbial translocation markers in PLHIV with physical functional performance and frailty, found that functional impairment (assessed via a composite Frailty Phenotype and the Short Physical Performance Battery [SPPB]) during successful HAART was associated with higher CD8+ T-cell activation and IL-6 levels. Furthermore, Erlandson et al.[95] demonstrated that increased

inflammatory markers (IL-6 and high-sensitivity CRP) were associated with frailty in PLHIV. In fact, it seems that frailty, not HIV serostatus, is associated with inflammation, as demonstrated by studies incorporating HIV-seronegative control groups.[95] Although harmful behaviours and comorbidities have been shown to account for much of the immune activation in PLHIV, CRP levels (regulated by IL-6) seem to remain elevated in those with frailty independent of these factors.[96]

2.3.2. HIV-Associated Non-AIDS (HANA) comorbidity

The following subsections review the literature explaining the increased risk in PLHIV for specific body system involvement and co-morbidity which may impact on motor function.

2.3.2.1. Central nervous system (CNS)

HIV-1 damages the blood-brain barrier via paracellular and transcellular mechanisms, with subsequent HIV-entry into the CNS within days of infection.[97] While no evidence exists for cytolytic HIV-infection of neurons, indirect local damage results from specific viral proteins (e.g. gp120, Tat, or Vpr) produced by infected cells.[12] Several aetiologies have been suggested to underlie the continuing HIV-associated neurostructural alterations despite controlled viraemia, such as permanent pre-HAART brain injury, chronic subclinical neuroinflammation,[98] drug neurotoxicity,[99] various HANA conditions[100] as well as virus-associated neurodegenerative processes similar to those seen in ageing.[101]

Diffuse CNS degeneration has been reported in chronic HIV infection, involving the frontal lobes, basal ganglia, cerebellum and pons.[33,101–104] A recent meta-analysis of HIV neurostructural studies (including reports from 1993 to 2016)[100] found that HIV-1 was associated with reduced total brain volume and grey matter volume (both cortical and subcortical), along with collateral cerebrospinal fluid volume increases, although modern HAART seems to have substantially reduced these macroscopic neurostructural changes. This regional CNS structure atrophy may be associated with established or progressive motor impairment.[100]

Changes in white matter, including pontocerebellar tract integrity deficits, have been demonstrated in PLHIV by structural magnetic resonance imaging (MRI) studies. Such changes were associated with static postural instability and impaired tandem walking (especially with eyes closed), as well as psychomotor slowing.[33] Postural instability in PLHIV has also been associated with cerebellar pathology. Axonal injury (even without myelin damage) or primary idiopathic cerebellar atrophy has been cited as potential mechanisms.[33]

HIV may also affect the basal ganglia,[105–108] although perhaps less severely so in recent times.[100] Apart from motor slowing, clinical manifestation of basal ganglia involvement includes voluntary movement impairment and compromised executive function. A South African study[104] found that HIV infection is associated with specific dysfunction of the more basic basal ganglia/putamen functions during reactive inhibition of voluntary movement, while more normal higher cortical functioning during proactive inhibition were evident. The authors suggested that HIV infection may thus mostly involve basic striatal-mediated motor execution control processes.[104]

Hakkers et al.[101] noted in their systematic review of the effect of HIV infection on brain function (measured by blood-oxygen-level dependent [BOLD] functional magnetic resonance imaging) that, even without clinical signs or symptoms (e.g. impaired neuropsychological test performance), PLHIV present with an altered amount of functional brain activation (mostly fronto-striatal) as measured by BOLD response. These authors offered the "brain reserve theory" as a possible explanation. This involves using more neural effort (due to hyperactivation or activation of adjacent structures) to achieve the same "normal" behavioural results.[109] PLHIV may hyperactivate some brain areas and recruit additional brain areas to maintain the same physical performance. However, this mechanism may fail under more challenging task conditions.[101] This inefficiency of hyperactivation is possibly due to HIV-1-related interfering processes (involving specific viral proteins produced by infected cells), such as compartmentalisation of HIV in the CNS and associated local persistent neuro-inflammation, or HAART toxicity (especially Efavirenz).[101]

2.3.2.2. Peripheral nervous system (PNS)

Current HAART regimens are less neurotoxic versus older regimens, and so there is a lower risk of developing peripheral neuropathies.[25] However, the prevalence of HIV-1 related distal symmetric polyneuropathy (DSP) remains high.[26–29] Risk factors for DSP in PLHIV include ageing, HAART regimen, longer HIV infection duration, and substance abuse.[110] Two potentially neurotoxic mechanisms are mostly described regarding the pathophysiology of DSP: neurotoxicity resulting from the virus itself; as well as neurotoxic adverse effects of HAART.[111] Although neuropathies resulting from viral or HAART mechanisms are clinically indistinguishable, different pathophysiologic processes have been implicated.[111]

Clinical signs and symptoms of DSP include a combination of reduced ankle deep tendon reflexes and sensory deficits in the distal extremities, paraesthesia, dysesthesia, and symmetric stocking–glove pain distribution.[111] Reduced levels of self-reported lower extremity

function have also been described.[110] Additionally, associated balance and gait impairments may be observed[112] although it seems that lower limb neuropathy does not necessarily account for postural instability in PLHIV.[113] It has been suggested that locomotor impairments in PLHIV may be more related to CNS dysfunction rather than the PNS (at least regarding the specific outcomes assessed) since some studies failed to find associations between motor performance and peripheral neuropathy, whilst others often required eyes-closed conditions to elicit group differences in postural balance.[2,33,113–115]

2.3.2.3. Lower limb musculature

Although still present in PLHIV, muscle wasting is less problematic since the introduction of HAART compared to the pre-HAART era.[116] The persistent occurrence of muscle wasting, including sarcopenia, in about 30% of PLHIV[44] may in part reflect high systemic concentrations of inflammatory cytokines leading to increased energy expenditure and proteolysis.[117] Notably, the initial loss of muscle mass associated with untreated HIV-1 infection may not fully recover even after establishing effective HAART.[118] This failure to completely restore muscle protein synthesis to normal is possibly due to an inability to completely eliminate the suppressive effects of factors associated with high viral loads (e.g. HIV-1 accessory protein Vpr) on muscle amino acid metabolism.[119] Furthermore, HAART-treated PLHIV may develop T-cell-mediated inflammatory myopathies (such as Inclusion body myositis and polymyositis – broadly characterised by proximal muscle weakness and quadriceps atrophy) related to immune restoration or drug-induced mitochondrial toxicity, especially with zidovudine treatment.[116]

Although appendicular muscle mass losses in PLHIV are associated with functional impairments,[120] dynapenia (loss of muscle strength and power) may contribute more to functional decline.[121] A study by Neto et al. found that 50% of PLHIV with undetectable viral loads had poor lower limb muscle performance.[122] Dynapenia may specifically affect the quadriceps muscles of PLHIV,[121] is associated with functional deficits such as poor chair-rise-time[123] and a South African study noted that lower limb weakness, particularly of the proximal muscles, impacts on self-perceived function in PLHIV.[44] The impaired central activation observed in PLHIV appears to be related to disease progression, as a stronger association has been noted with viral load and AIDS-defining disease history than with HAART medications.[121]

Cardiovascular fitness impairments are known to occur in HAART-treated PLHIV.[124] Therefore, deconditioning may also contribute to intra-muscular deficits, including fatty muscle infiltration, and a poorly understood impairment of central coordinated motor unit activation

(the ability to activate the available muscle mass and a component of dynapenia) noted in PLHIV.[121,124,125] Oxidative stress/impaired oxygenation and mitochondrial toxicity (which may affect intramuscular calcium-handling processes and limit muscle oxygen extraction-utilisation) constitute widely-reported pathological processes underlying muscle weakness and fatigue in PLHIV, particularly those on HAART.[32,126] Specifically, PIs and NRTIs (such as tenofovir and abacavir) have been associated with mitochondrial myopathies.[126] A premature and upregulated expression of genes associated with muscle ageing has been described in middle-aged (30 to 55 years old) male PLHIV (and not seronegative controls), with a prominent fibrotic axis.[127] The authors noted this chronic inflammation-driven muscle fibrosis as an understudied potential mediator of functional decline in PLHIV.[127]

Despite the cited research, results regarding significant lower limb muscle *strength* differences *per se* between PLHIV and their HIV seronegative counterparts remain controversial and studies are often limited by small sample sizes, unequal gender distributions or cross-sectional design. Oliveira et al.[128] reported differences in dynamic and isokinetic strength in male PLHIV versus SNP, but not in female participants. The authors attributed the observed differences to the presence of comorbidities and impaired muscle activation; however, the study was limited by a small sample size. Similarly, a South African study[129] noted that lower limb muscle strength was not significantly different between female PLHIV and SNP. The similarities may have been due to the controlled viraemia and good general health of participants. In contrast to Oliveira et al.[128], two cross-sectional studies[130,131] found similar musculature and strength between male PLHV and SNP. Wallet et al.[130] partly attributed the observed similarities in lower limb muscle morphology and strength to the well-controlled disease markers, despite strong evidence for increased inflammation noted in the HIV-1 group. Raso et al.[131] found similar peak aerobic power and muscle strength when comparing groups, apparently uninfluenced by CD4+ nadir or HAART-use, although isokinetic strength was lower in those PLHIV with current low CD4+ counts. These studies were all conducted in middle-aged cohorts of virologically-controlled PLHIV on HAART, and were all limited by small sample sizes.

2.3.2.4. Bone status

Earlier and a higher rate of osteopaenia and osteoporosis is evident in PLHIV,[132] with a prevalence of resultant fractures.[132–136] Emerging research regarding increased fracture rates in PLHIV report rates of 30% to 70% higher in PLHIV compared to seronegative controls[137]; and a 38% increased risk for hip fractures in PLHIV.[136] Low BMD, in addition to lower limb

impairment (including sarcopenia), is associated with balance problems and increased fall risk.

HIV-associated reductions in bone size, mass and strength have been attributed to altered metabolism and infection of bone cells,[86] HAART exposure (e.g. tenofovir disoproxil fumarate [TDF]) and additional risk factors have been cited including smoking, substance abuse (especially alcohol), sedentary lifestyle, low body weight, menopause and vitamin D deficiency.[86] A meta-analysis[135] reported the prevalence of osteopaenia and osteoporosis in PLHIV as 67% and 15% respectively.

It has been suggested that uncontrolled viraemia may impact BMD, possibly mediated by effects of persistent systemic inflammation on bone remodelling; this is evident as osteopaenia and osteoporosis is highly prevalent in HAART-naïve (i.e. not previously exposed to HAART) PLHIV.[132] HIV-proteins impair bone formation by promoting both osteoclast activity and osteoblast apoptosis.[86] In addition, elevation of tumour-necrosis factor-α (TNF α) promotes bone resorption mediated by osteoclasts, without collateral bone formation increases.[132] However, relationships between BMD and HIV duration, viral load, or CD4+ count has not been consistently observed.[138]

HAART initiation seems to amplify bone loss and is typically followed by a 2% to 6% BMD reduction (the largest losses occurring within 24 to 48 weeks).[86,138] Subsequent plateauing is reported by various studies, although follow-up was mostly less than three years.[132,138] All ART seem to decrease BMD, although greater reductions have been observed with the use of TDF and ritonavir-boosted PIs. Although the exact reason for BMD loss after HAART initiation remains unclear, it has been attributed to increased bone catabolism after viral load suppression and immune reconstitution,[138] and it has been suggested that activation of CD4+ cells along with immune reconstitution after treatment lead to higher levels of pro-inflammatory, pro-resorptive cytokines.[134]

Although BMD loss seems to be largely irreversible,[86] a 2018 systematic review by Chisati et al.[139] found that research is lacking and that it may be worth investigating effective non-pharmacological interventions to prevent and treat BMD loss in PLHIV on HAART. Pharmacological regimens (e.g. bisphosphonates, teriparatide, denosumab) are unfortunately often associated with adverse reactions (e.g. tumours, infection, osteosarcoma and bronchitis) and increase the pill burden in PLHIV; negatively affecting adherence and limiting their effectiveness.[139] Exercise-based strategies to mitigate decreased BMD resulting from HAART, such as progressive resistance exercise, have been suggested as a safe and effective

alternative approach that could be used to manage bone loss resulting from ART in PLHIV – although at present only one such study has been identified from the literature.[139]

2.3.2.5. Metabolic and endocrine complications

Metabolic diseases, including type II diabetes mellitus, dyslipidaemia, obesity, and the metabolic syndrome are becoming more prevalent among PLHIV in high- and low-to-middle income countries alike.[32,70,140,141] These disorders often occur in concert in PLHIV and may share underlying pathogenic features. BMD and frailty status amongst PLHIV have been reported to be substantially affected by metabolic disorders and resultant changes in body composition.

The functional consequences of a change in body composition in PLHIV were first investigated by Shah et al.,[140] who proposed a new frailty phenotype in PLHIV that is associated with obesity rather than the traditional observation of wasting. The study data suggested that excessive hypertrophy of visceral fat and lipolysis contribute to fat infiltration in the muscle, and consequently reduces muscle quality and a decline in physical function among PLHIV.

2.3.2.6. Neuromotor impairments associated with HIV-1

Movement disorders are conspicuous in the constellation of impaired function in PLHIV.[2] The association of motor impairments and function was demonstrated early-on (1996) by The Dana Consortium on Therapy for HIV Dementia and Related Cognitive Disorders.[142] In a cohort of 271 PLHIV (mean ages ranging from 38 to 41 years), it was demonstrated that it was rare to have functional impairment (as measured by the MOS-HIV physical function domain) without associated neuromotor deficits.[142]

Neurocognitive impairments have historically been associated with HIV-1 infection. However, over the last couple of decades, the increasingly widespread availability of HAART has changed the clinical features of HIV-associated cognitive syndromes and studies have started to separate the entities of cognitive impairment and motor impairment, whilst acknowledging that clear associations do exist.[143] Although the prevalence of motor deficits has still not been sufficiently examined in the current treatment era,[144] it is estimated that 35% to 70% of all PLHIV (HAART and HAART-naïve) are at least subtly impaired on neuropsychological assessments, which includes motor function.[145–148]

In 2008, the first objective assessment tool of motor deficits traditionally associated with HIV-associated neurocognitive disorders (HAND) was developed.[143] These deficits included,

amongst others, movement slowing, gait impairments and uncoordinated limb movements. The authors[143] developed this tool in recognition of the fact that motor abnormalities remained prevalent and of clinical importance in the HAART era despite the relatively milder presentations of HAND.[143] The tool revealed that motor abnormalities (for example strength deficits, gait and coordination problems, tone and reflex abnormalities) can predict cognitive impairment in PLHIV.[143] Ten years later, the authors longitudinally re-explored motor dysfunction in medically complex PLHIV with ages ranging from 29 to 80 years (mean age 52 years) and found that motor function (including gait) declined over time and was accompanied by an accrual of comorbid medical illnesses.[144] However, over a four-year period of assessment, no significant decline in cognitive function was observed. The authors emphasised the importance of the accumulation of motor impairments, as motor impairment substantially impacts on successful ageing and maintenance of independence.[149]

Joska et al.[26] conducted the first South African descriptive follow-up study to establish the effects of HAART on neuropsychomotor impairment among a group of PLHIV. Adults (median age 30 years) in late stage HIV-1 infection and commencing HAART were prospectively investigated. Participants with severe impairment at baseline improved significantly in various domains, including gross motor speed and fine motor function, within a one-year treatment period. However, mild to moderate neuro-motor impairments persisted in a quarter of the sample, emphasising that HAART does not completely reverse these effects.

2.4. A model of accelerated or accentuated ageing?

There is an emerging trend amongst researchers and clinicians to use terms such as “accelerated ageing” or “accentuated ageing” when referring to the plethora of HIV-associated comorbidities, given that many of these diseases are usually age-associated in the general population and observed in elders. Yet whether HIV truly causes premature or advanced ageing remains controversial.[64,70,150] It has been questioned whether HIV physiologically hastens ageing processes in general or whether HIV acts as a factor to synergistically increase the risk of developing illnesses such as cardiovascular disease at any age in PLHIV.[151] In addition, cohort studies investigating ageing effects in PLHIV have often not included appropriate comparison groups to enable meaningful conclusions.[152]

However, the similarities between HIV-1 and the normal ageing process are compelling. Arguments stating that there may be a biologic plausibility of HIV-1 causing accelerated ageing has pointed out the similarities between the pathophysiology of treated HIV-infection and the general process of ageing, including the prognostic value of a low CD4:CD8 ratio, telomere

shortening, immunosenescence manifestations, oxidative stress, chronic inflammation and hypercoagulability, ongoing immune activation and the roles of coinfections such as cytomegalovirus.[64,65,70,153] In addition, multi-morbidity, geriatric syndromes, polypharmacy, as well as traditional risk factors are prevalent in older but also middle-aged PLHIV. These factors may all contribute to the increased risk of developing the clinical manifestations of ageing in the general population and presumably earlier, or in an accentuated manner, in PLHIV.

Of course, data from high-income countries related to biological ageing and HIV may not be directly translatable to low-to-middle income countries, as biological ageing in PLHIV in such resource-limited settings can also be affected by lower socioeconomic status, malnutrition, coexisting morbidities, opportunistic coinfections and epigenetic variation.[154] Yet a case-control study[154] assessed biological ageing in South African PLHIV (median age 39 years) and HIV-seronegative individuals (median age 40 years) and found increased biological ageing in PLHIV (after adjusting for age, gender and other confounders) confirmed by two validated biomarkers. Also, a study by Horvath and Levine[155] observed epigenetic age acceleration as early as adolescence in a cohort of Capetonian adolescents living with HIV-1 infection (mean age 10 years); and that these epigenetic changes were associated with poorer cognitive functioning. Keeping in mind the controversies, the similarities observed between HIV infection and ageing are intriguing and imply that valuable insights may be gained from the geriatric literature, that is likely to usefully inform research and rehabilitation strategies in PLHIV.[53,156]

2.5. HIV-1 infection and falls

Despite a large research focus on the interactions between HIV-1, HAART and low BMD, the risk of falls in PLHIV has not yet been adequately described. A quick exploratory PubMed search in June 2018 revealed over 5 000 publication citations in reference to “HIV and bone”. In contrast, only 22 PubMed citations included “HIV” and “accidental falls” and only nine of these hits reported rates of falls or characteristics of HIV-infected fallers – these studies are summarised in Table 2.2.

The first study to report the rate and risk factors for falls among PLHIV was published in the USA in 2012.[55] Results indicated that 30% of study participants aged 45 to 65 years had fallen in the previous year (a rate similar to HIV-seronegative persons aged 65 years or older). Subsequent studies consistently note falls among middle-aged PLHIV, but report varying rates ranging from 1.6% to 41% (Table 2.2). Notably, the three studies that included HIV-seronegative controls[157–159] found similar fall rates in PLHIV and HIV-seronegative controls after adjusting for covariables. These observations may reflect that PLHIV and the HIV-

seronegative participant groups were demographically similar regarding the overall burden of fall risk; whereas more significant results (as in Erlandson et al.[55]) may be due to the fact that comparisons were made using normative data obtained from a different demographic. The lower fall rates in Sharma et al.[160] and Erlandson et al.[158] compared with the other studies may be explained in part by volunteer bias (healthier individuals agreeing to participate), and the very low rate in Ruiz et al.[161] may be due to potential underreporting among healthcare providers who completed the patient records.

Falls are the consequence of multiple interrelated factors. In PLHIV, common risk factors for falls include frailty[iii],[162,163] peripheral neuropathy,[159,162] functional impairment (e.g. slowed gait, grip strength deficits [a good predictor of general muscle strength] or impaired balance symptoms),[55,162] multimorbidity,[55,161] and polypharmacy[55,157,161,164]; although it seems unclear whether these risk factors are unique to PLHIV. In contrast to the strong associations between HIV-specific factors and low BMD discussed in Section 2.3.2.4 of this review, HIV-disease markers appear to have minimal effect on fall risk. However, falls pose a particular concern for PLHIV because of their reduced BMD, and the fact that many risk factors for falls and BMD overlap, translating to a compounded high risk of fractures secondary to falling.

[iii] *Frailty refers to a clinical state (syndrome) of greater vulnerability due to dysregulated reserve and function across various physiologic systems, compromising the ability to cope with everyday stressors. Frailty is often operationally defined according to Fried's phenotype.*[53]

Table 2.2. Summary of studies reporting falls in people living with HIV-1 infection (PLHIV).

	Erlandson 2012[55]	Ruiz 2013[161]	Greene 2015[52]	Sharma 2016[160]	Erlandson 2016[158]	Tassiopoulos 2017[162]	Kim 2018[164]	Ssonko 2018[163]	Sharma 2018[159]
Design	Cross-sectional.	Retrospective review.	Cross-sectional.	Cross-sectional.	Cross-sectional.	Prospective, multicenter cohort study.	Secondary analysis.	Cross-sectional.	Longitudinal.
Country	USA	USA	USA	USA	USA	USA	USA	Uganda	USA
Aim	To investigate whether increased fall risk factors would increase fall rates among middle-aged PLHIV.	To investigate fall incidence and risk factors in PLHIV.	To describe geriatric syndromes in PLHIV aged ≥50 with undetectable VL.	To determine fall frequency and risk factors among middle-aged women with HIV and HIV-controls.	To (1) compare fall rates in PLHIV or adults at risk for HIV, (2) determine if HIV infection is an independent fall risk, and (3) determine other fall risk factors potentially unique to HIV.	To investigate frailty-to-fall risk among PLHIV.	To determine whether polypharmacy is associated with falls and fractures among PLHIV and substance dependence or injection drug use.	To determine polypharmacy prevalence, associated factors and whether polypharmacy was associated with adverse effects among older PLHIV on ART.	To determine the longitudinal occurrence and risk factors for falls in women with HIV, and explore associations with cognition.
Fall definition	Using slightly varying terminology, all studies but one included the following: "Unintentionally/unexpectedly coming to rest on the ground or other lower level". One study[164] included falls caused by an external hazard while seven studies used the qualifier "*not* as a result of a major intrinsic event or external hazard". One study[163] did not mention their definition of a fall.								
Falls assessment	All studies (except the two longitudinal follow-ups) used retrospective self-report (history of one or more falls during past 12mo). Sharma et al.[159] and Tassiopoulos et al.[162] used semi-annual retrospective self-report at each study visit starting at 6mo follow-up (history of falls since previous visit).								
Sample description	PLHIV aged 45 to 65 years, receiving effective ART.	Patient records of PLHIV from an academic urban HIV clinic, who fell during prior 12mo.	PLHIV from SCOPE cohort aged ≥50 years, on ART with undetectable VL.	HIV+ and HIV- WIHS participants with available falls data.	HIV+ and HIV- men and women participating in the Hearing and Balance Substudy of	HIV+ men and women aged ≥40 years.	PLHIV with substance dependence or injection drug use, from Boston ARCH Cohort study.	Older PLHIV on ART aged ≥50 attending an outpatient HIV/AIDS care centre.	HIV+ and HIV- WIHS participants with available falls data and attending

					the MACS and WIHS.				semi-annual study visits.
Sample size	359	32	155	2062 (1 412 HIV+ and 650 HIV−)	536 (303 HIV+ and 233 HIV-)	967	250	411	1 816 (1 250 HIV+; 566 HIV-)
% women	15%	25%	6%	100%	Mostly men.	Mostly men.	38%	58.2%	100%
Average age in years	Mean age 52 ± 0.30	Average age 48.19	Median age 57 (IQR 54–62)	Mean age 48	Median age HIV- 54.90; median age HIV+ 49.70	Median ages ranged from 50 to 53	Median age 50 (IQR 44-56)	NR, but sample included participants aged 50 to >65	Median age HIV+ women 49; median age HIV- women 47
HAART	100%	100%	100%	88%	69%	100%	100%	100%	88%
Viral load	95% had VL <LDL.	Mean VL 31 379 copies/mL.	100% had VL <LDL.	65% had VL <LDL.	69% had VL <LDL.	NR	72% had VL <LDL.	NR	63% had VL <LDL.
Main results	70% reported no falls, 30% had ≥1 fall; 18% were recurrent fallers. Females, Caucasians, didanosine-recipients and smokers were more likely recurrent fallers. HIV-related characteristics were not predictors of falls. Multimorbidity, medications, functional impairment and balance	32 faller cases identified from 2000 records (1.6%). Univariate and multivariate analysis showed that number of medications, >3 comorbidities and noncompliance were related to falls.	25.8% of participants reported ≥1 fall. Median fall count was 2 and 12.5% reported an injurious fall requiring medical attention.	≥1 fall reported in 19% HIV+ vs. 18% HIV- women; ≥2 falls reported in 9% HIV+ vs. 10% HIV- women. HIV infection not associated with falls. Factors independently associated with any fall were age, current marijuana use, depression, cognitive complaints, PN, obesity, number of CNS active	≥1 fall reported in 24% of PLHIV vs. 18% of HIV-. PLHIV were more likely to report imbalance symptoms. Smoking, polypharmacy, and imbalance remained independent fall predictors in PLHIV. Current PI use was protective.	18% had ≥1 fall, and 7% had recurrent falls. In multivariable models, pre-frailty and frailty were associated with recurrent falls. Significant associations were also seen with recurrent falls and slowed walk and weak grip. The association between frailty and falls was stronger among i	In PLHIV/substance dependence, a higher number of systemically active medications was associated with greater odds of having a fall requiring medical attention. The association appeared to be driven largely by sedating medications.	Polypharmacy was not associated with falls. Frailty and mild and moderate cognitive decline were significantly associated with falls in multivariate analyses. Current PI use was associated with falls.	≥1 fall reported in 41% HIV+ vs. 42% HIV-, including ≥2 falls in 25% HIV+ and 24% HIV-. Factors associated with falls included: depression, PN (HIV+ and HIV-); age, marijuana use, multiple CNS medications, HCV infection (HIV+ only).

	difficulty predicted falls.			agents and study site.		individuals with PN.			
Adjustment for covariates	All studies reported extensively on the various relevant variables that were adjusted for, including demographic, HIV-related, clinical, medication-related and general health variables. The reader is referred to the individual texts for detailed lists.								

Abbreviations: ARCH = Alcohol Research Collaboration on HIV/AIDS; ART = antiretroviral therapy; CNS = central nervous system; HCV = hepatitis C virus; LDL = lower than detectable limit; MACS = Multicenter AIDS Cohort Study; mo = months; PI = protease inhibitor; PLHIV = people living with HIV-1 infection; PN = peripheral neuropathy; SCOPE = Observational Study of the Consequences of the Protease Inhibitor Era; USA = United States of America; VL= viral load; WIHS = Women's Interagency HIV Study.

2.6. The conceptualisation of HIV-1 into a framework of rehabilitation

Rehabilitation has been declared by the WHO as the key health strategy of the 21st century.[165] This is in acknowledgement of the fact that the sequela of survivorship with an increasing burden of chronic diseases (HIV included) involve limitations in functioning and participation. A new paradigm in HIV management is increasingly advocated[166,167] with the aim to maximise functional status, minimise functional decline, and optimise quality of life over the extended life years of PLHIV.

The changing face of HIV and its presentation has led to the reconceptualisation of HIV from a biomedical model into a rehabilitation framework.[167,168] Attention has shifted towards the related "impairments" (body structure or functional deficits), "activity limitations" (problems at the whole-body level) and "participation restrictions" (difficulties related to the individual and their environment); as defined by the WHO's International Classification of Disability, Functioning and Health (ICF) (see Figure 2.2).[169]

The concept of rehabilitation in the context of HIV is still emerging,[170] but already the role of rehabilitation specialists such as physiotherapists are increasingly advocated in the management and prevention of HIV-related disability; both locally and internationally.[171,172] In illustration of this trend, the South African Society of Physiotherapy (SASP) has recently aligned itself with the South African Department of Health in achieving the National HIV/AIDS and STI strategic plan, by emphasising HIV care within physiotherapy practice.[173] In a further example, an open-access online resource on rehabilitation for PLHIV in Canada has recently been adapted for Sub-Saharan Africa (http://ssa.hivandrehab.ca/).[174]

Rehabilitation is a field designed to aid individuals in addressing challenges to function and well-being, and thus plays a role in the lives of people living longer with HIV and experiencing motor impairments. In this dissertation, when referring to rehabilitation, it is done with reference to the definition by Worthington et al.,[168] namely that it is a dynamic process and includes any treatment activities and/or services that may tend to or prevent impairments, activity limitations or social participation restrictions experienced by an individual. There is a need to engage in research in Sub-Saharan Africa that explores rehabilitative care, especially in terms of early screening and prevention of functional impairments, as a cost-effective means of improving well-being and quality of life for all PLHIV experiencing (or at risk for) disability.

2.7. Defining function

The ICF uses the umbrella term "functioning" to describe body structures and functions, activities, and participation.[169] "Disability", on the other hand, describes compromised functioning by referring to impairments (a loss or abnormality in an anatomical structure or physiological function), activity limitations ([in]ability to execute a task or action) and participation restrictions ([non]involvement in life situations within society).[169] Environmental and personal contextual factors may extenuate or aggravate disability.[169]

Impairments may manifest at the body structure level as, for example, motor- or muscle function deficits and impaired joint mobility. Such impairments, individually or combined, may contribute to activity limitations and eventually, a trajectory towards functional decline and disability.[175]

In the geriatric literature, declining physical and cognitive function is commonly termed "functional decline". Beaton at al.[176] described functional decline as an insidious onset, complex manifestation of ageing; easily overlooked in its early stages. These authors extensively explored the complex domains and constructs underlying early functional decline in the general population. Performance capacity was identified as one of the (many) domains of functional decline, including physical constructs such as balance, chair rise, gait speed, step length and more.[176]

The term "functional decline" has been used interchangeably in the HIV literature as referring to frailty or disability, to indicate decreases in physical function performance or self-reported function or a combination of functional domains. To the author's knowledge, no formal reference has been made in the HIV literature to the proposed definition of functional decline as it is used within geriatrics, although it mostly seems to intuitively refer to reductions in physical and/or cognitive function performance in the patients studied. Throughout this dissertation, the concept of function is used to describe body functions, body structures, and activities alike and "functional decline", as used in this dissertation, relates to deteriorations in these functions.

Figure 2.2 presents the ICF model as applied to chronic HIV-1 infection and illustrates how some of the specific variables of interest (or contributors to motor function) in this study interact within the ICF framework, and the potential consequent influence of such interactions on activity limitations, physical functioning and social participation.

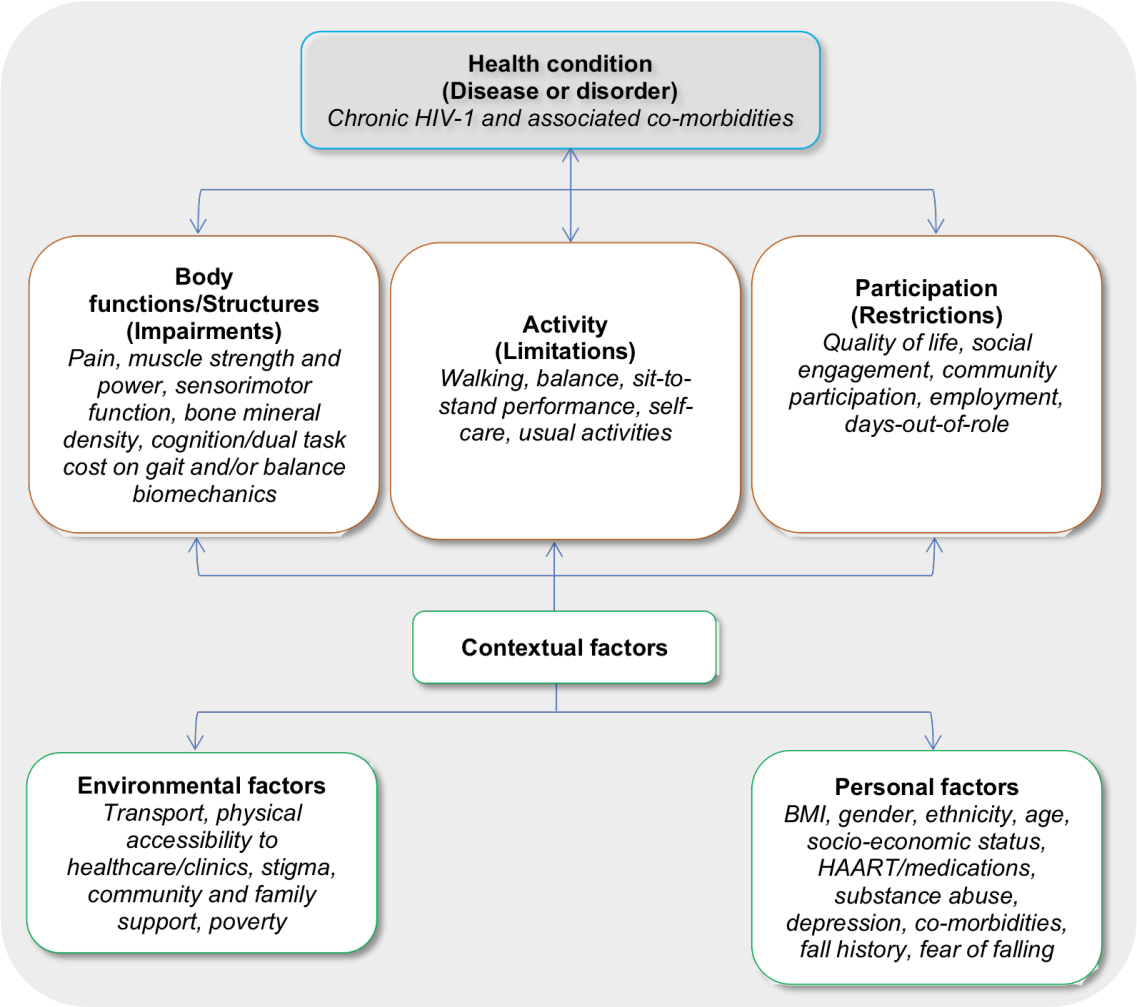

Figure 2.2. The International Classification of Functioning, Disability and Health (ICF) model as applied to chronic HIV-1 infection.

2.8. Assessing lower limb impairments and function

2.8.1. Objective (clinical performance) and subjective (patient-reported) outcome measures

Given that (i) even virologically-controlled PLHIV commonly demonstrate some degree of lower limb impairment at earlier-than-expected ages,[2,38,51] (ii) the fact that many functional activities depend on the integrity of lower limb neuromusculoskeletal structures,[49] and (iii) the importance of lower limb function in predicting future disability;[49,50] early assessment of lower limb function in chronic HIV may be of value. Indeed, to better understand health in chronic diseases, it is important to extend assessment beyond conventional disease measures, and use clinical assessments of function.[177,178] Measurement of impairments or functional limitations using either self-report (which is an evaluation

of perceived dysfunction) or standardised objective measures of physical performance (such tests mostly measure impairments or functional limitations) is crucial for understanding the dynamics of the functional pathway leading from disease to early functional decline and disability.[177,179] The concept of a preclinical transitional phase existing in the trajectory of functional decline (i.e. early, subtle losses in function which act as precursors to disability) in the general population was first prospectively tested by Fried et al.,[178] using a cohort of high-functioning older adults with no mobility-related disability at baseline. These authors confirmed that early declines in function can be identified by self-report[180] and objective performance measures,[181] and that both are (complementary) predictors of incident disability. Self-reported function was found to correlate better with impairments and physical performance tests (i.e. clinical tests of impairments and functional limitations) than with underlying disease status[180]; with those participants reporting modified activities (i.e. preclinical declines in function) demonstrating a high risk of incurring mobility-related disability over 18 months. These findings support the predictive validity of self-perceived function at the stage of preclinical disability.[iv] However, self-report and objective assessments are considered complementary and both have been shown to predict outcomes, although they may not always measure the same physical function constructs.[156,178,180]

It is evident from the literature reviewed thus far that PLHIV experience non-AIDS-defining complications, resembling geriatric processes[52,53] and that this hypothesised accelerated or accentuated ageing may manifest in middle-aged PLHIV as neuromotor impairments and low BMD. Such impairments are associated with balance problems and increased fall risk.[2,55] A response to the shift in HIV survivorship was to reconceptualise HIV into a rehabilitation framework, and assessments of physical (lower limb) function based on geriatric principles may prove useful tools for HIV clinicians and researchers to help identify those at risk of functional decline. Walking speed is a predictor of preserving independence with ageing[182] and may be easily derived using short walk tests (e.g. six metres) and a stopwatch. The Short Physical Performance Battery (SPPB) is another widely validated and used physical functional measure in older adults.[183] It measures various aspects of lower limb function such as balance (static and dynamic), lower limb muscle performance and gait speed. Performance on each of these aspects are then merged into an overall physical function score with a maximum of 12 points. SPPB score predicts problems with activities of daily living, as well as the existence of disability in community-dwelling older adults.[50,184] For example, small

[iv] *Preclinical disability involves progressive loss of function and refers to an intermediate phase prior to the onset of disability. The individual does not yet identify as experiencing impairment or disability in everyday tasks but adapts (consciously or unconsciously) the frequency or manner in which the task is completed so that they may function optimally.*[178]

improvements in gait speed (differences >0.05 m/sec) and SPPB performance (differences >0.5 points) translate to meaningful improvements in ADL.[185]

Functional assessment in PLHIV may help to understand the impact of the concomitant processes of ageing, HIV-1 infection and its treatment, comorbid diseases and lifestyle on successful ageing and preservation of independence[59] and measures from geriatrics have indeed been proposed to be of clinical use in middle-aged and ageing PLHIV.[2,3,53,58–60,156] For example, the SPPB has been used in multiple cross sectional HIV studies and proved to be associated with mortality[60] and fall-risk.[55] Schrack et al.[58] reported a faster rate of functional gait speed decline in male PLHIV versus seronegative controls, suggesting greater risks of disability and death with advancing age. Selecting the most appropriate test depends on the desired measurements and goals of assessments including correlations with lower limb tasks, measuring strength, or assessing fall risk.[156]

It should be noted that a physical performance-based test does not necessarily correspond to a loss in function, as it often does not render information beyond *what* a person is able to do (as opposed to *how* they do it); potentially limiting such tests to predict functional consequences.[179] This is unfortunately a limitation of all clinical testing, and an ongoing area of investigation.[179] Nonetheless, functional limitation tests substantially contribute to knowledge about patient populations[156] and are practical for implementation in the clinical setting. Further research is thus warranted to assess and promote their utility and standardisation in HIV research and clinical settings alike.[177]

2.8.2. Considerations for PLHIV

It is important to keep in mind that even when traditional geriatric assessments are used in (younger- or older-age) PLHIV, results may be different than in the general population of elderly.[156] In their comprehensive review of functional and geriatric assessment in PLHIV, Greene et al.[156] illustrated that a different pattern of disability or functional decline may manifest in middle-aged or younger adults dealing with complex chronic illness and social situations compared to the general population of older adults. Ongoing studies of specific assessments from geriatrics applied to, and potentially modified for, PLHIV are needed.[156]

As the population of PLHIV is still predominately young to middle-aged in Sub-Saharan countries, assessments in these contexts should be tailored to test a higher level of function.[53] Objective assessment of functional limitations to capture the subtler spectrum before full disability (like an expanded and more challenging SPPB) may for example be appropriate. Additionally, the use of dual task activities[186] has been advocated but not yet widely applied. The performance difference between single- and dual tasks represent the demands placed on the processing system when attention is divided between two tasks simultaneously, and thus may be used as an indication of the

attention demands (cognitive compensation) required by the primary task.[187] In PLHIV, this might reveal more subtle movement impairments in higher functioning individuals.[186] These techniques may be especially relevant in studies which include PLHIV under the age of 50, as is the case in this project.

2.8.3. Instrumented (quantitative) assessment methods

Three-dimensional (3D) instrumented motion analysis provides sensitive, accurate and comprehensive data on normal and pathological functional movements such as walking gait. Instrumented motion analysis is one of the few measurement approaches that quantifies functional limitations, with analysis allowing insight into the dynamic implications of a particular impairment such as muscle weakness.[61] As the technology supporting the 3D analysis of human motion has advanced dramatically over the past couple of decades, in-field quantitative gait analysis by means of lightweight, compact, portable motion capture systems has become a possibility for collecting kinematic data and is now proposed as a clinically useful tool.[188,189]

Instrumented motion analysis outcomes have been emphasised as markers of function in various patient populations such as neurological,[190] musculoskeletal,[191,192] and endocrine[193] conditions, as well as in the elderly,[194] people at risk for neurocognitive dysfunction,[195] and fallers.[196,197] For example, in the elderly, increased accuracy of fall prediction models based on common clinical fall risk assessment tests (fall questionnaires and physical performance tests such as the SPPB), has been demonstrated when gait measures from comprehensive gait analysis are included.[198,199] These authors found that gait analysis variables derived from trunk accelerometry may predict fall risk independently of physical performance.[198]

In PLHIV, abnormal gait patterns may be hypothesised to result from combined effects of a primary impairment, such as muscle weakness, and the secondary compensation for preserving locomotion as efficiently as possible.[200–202] The relationships between primary impairments and their locomotor manifestations, including secondary compensations, cannot yet be quantified from existing data on locomotion in PLHIV. However, based on the data reviewed thus far, one might expect the motor impairments in PLHIV to manifest biomechanically as a pattern of gait or balance control that resembles that of older adults and/or fallers. Comprehensive quantitative analysis of gait deviations in PLHIV may distinguish such pathologic patterns,[203,204] potentially helping to inform associations between pathologies, neuromusculoskeletal contributions, movement patterns and functional consequences.[203,205] Studies in other pathologies have investigated correlations of clinical instruments with spatiotemporal and kinematic variables. A study by Roiz et al.[190] demonstrated that some clinical tests (e.g. the motor Unified Parkinson's Disease Rating Scale [UPDRS], Timed Up-and-Go [TUG] Test and Berg Balance Scale [BBS]), correlate well with, and were thus able to

perceive, certain biomechanical alterations (e.g. ankle, pelvis and hip angular deviations) in Parkinson's Disease.

An important complexity of gait analysis is the inter-dependence of many gait variables.[201] Gait speed, for example, influences lower limb kinematics and increased joint ROMs are observed at faster gait speeds. This effect of gait speed depends on the specific angle and also on the phase of the gait cycle.[206] Knee flexion in stance and swing show particularly strong positive correlations with gait speed.[207] The effect of speed thus needs consideration when comparing gait data from patient populations walking at slower self-selected speeds than the comparison group by adjusting kinematics according to gait speed.[206] Comparing gait data without doing so makes it difficult to know whether reduced joint excursion is due to the slower gait speed, or co-occurring as an independent pathological feature. Another consideration is that individual gait patterns vary by age, anthropometrics, personality, mood and sociocultural factors: for example, people living in urban neighbourhoods or cities walk significantly faster than those living in rural settings.[208–210] Norms in a certain population may thus not necessarily hold true in individuals from different communities – highlighting the need for appropriate comparison groups in research studies. The comprehensive data provided by 3D motion analysis are therefore often not straightforward to interpret.

Effective rehabilitation of gait and balance impairments in PLHIV, as in other patient populations, largely depends on an understanding of the underlying deficits and their interactions. Given the knowledge gap regarding quantification of how PLHIV perform walking- and balance tasks, it seems that there is potential for 3D motion analysis to explore the uncertainties regarding the nature of locomotor impairment. It must be noted, however, that kinematic motion analysis presents the observer with *effects* and not *causes*. What is observed as a gait pattern, is therefore not a direct result of the pathological processes at hand. Rather, it is the net result of a complex interplay between causes and compensatory actions of the body[202] or the remnants following the exhaustion of all available compensatory mechanisms.[201] What this implies, is that the determination of causes require an initial theory, which then has to be tested by inflicting some interference to the system.[202] Although the 3D gait analysis performed in this dissertation did not involve additional measures (such as gait kinetics or electromyographic measurements) other than kinematic angles and TSPs of gait, the research assessed additional more challenging conditions over and above the baseline activities of walking at habitual speed and SLS with eyes open. Also, the literature was consulted regarding clinically relevant gait analysis outcomes (including key events and phases) for joint angles in the elderly and fallers to inform the conceptual framework underlying this research – these are presented in the following section.

2.8.4. Gait deviations indicative of advanced age and/or fall risk

The following sections review gait deviations indicative of advancing age and/or fall risk in the general population. Understanding the effects of normal ageing on locomotor function and lower limb gait biomechanics will contribute towards a conceptual framework for interpreting gait deviations in PLHIV; given the feasible similarities reviewed thus far. Such a framework may aid in confirming (or refuting) deviations resembling an elderly or fall-risk phenotype in young-to-middle-aged PLHIV.

Relative to younger adults, older adults tend to walk slow and with changes in their kinematics as well as their kinetics.[201,211–216] Reductions in total joint excursions are common.[217] Although such changes have been widely reported, the causes of the observed adaptations are not well understood.[218] This may in part be due to the difficulties associated with experimentally determining cause and effect in the study of human physiology.[218] Some previous gait studies in elders have failed to account for covariables such as gait speed when describing biomechanical differences between older and younger adults.[194] When controlling for gait speed, a normal gait pattern has been suggested in the elderly as compared to younger adults. For example, Ferrandez et al.[219] analysed gait parameters during different speed conditions in a group of 67 older adults (aged 60 to 80+ years) and young participants. The authors found that shorter stride and an increased double support phase were the main characteristics of elderly gait, but that these were likely speed-related, since similar characteristics were also observed in the young participants when asked to walk slowly. The study concluded that elderly gait is normal if gait speed is accounted for.[219]

2.8.4.1. Temporal, spatial, temporophasic and temporospatial parameters (TSPs)

Blanke and Hageman[220] found no significant differences in gait speed, step length or stride length between older and younger men. However, this study was limited by a very small sample size in terms of studying gait differences (n = 12 per group) and may thus have been underpowered to show statistical significance. In addition a 1% level of significance was chosen (a *p*-value of 0.01) which may have been too restrictive – as pointed out by Prince et al.,[221] *p*-values of 0.05[222] are traditionally selected for gait studies. Blanke and Hageman's paper[220] was one of the only studies failing to show a difference in gait speed between older and younger ages – indeed, one of the most consistent differences demonstrated is gait speed and multiple-regression analysis has demonstrated that age accounts for 30% to 45% of the variability in gait speed.[223] Oberg et al.[224,225] assessed basic gait parameters in 233 healthy participants aged 10 to 79 years, under slow, normal, and fast gait speeds. Using two-way analysis of variance (ANOVA) they demonstrated that age-variability was significant for gait speed and step length at usual-paced and fast speeds (reduced in elderly), but not for cadence. Step length showed a significant interaction effect of age and gender at normal and fast

speeds. Unfortunately, the study does not report on the health status of the participants, or method of recruitment. The validity of the gait speed conditions is also uncertain, as the authors fail to mention the specific instructions given to participants about the gait speed needed to be obtained (slow, normal or fast).

In addition to the studies already mentioned, various other studies have also reported shorter step length in older adults[226–229] although yet others negate this finding.[230,231] A review by Beijersbergen et al.[232] noted that shorter steps and slower gait speed may be the most functionally meaningful changes in elderly gait.

2.8.4.2. Kinematic variables

Both Winter[222] and Oberg et al.[224] found very small differences in joint angle patterns between younger and older adults, with subtle changes occurring in amplitudes. Oberg et al.,[224] in their sample of 233 healthy persons aged 10 to 79 years, demonstrated minor changes in lower limb joint angles with age, no differences between right and left legs, significant gender differences, and significant changes with increasing gait speed.

Dynamic ankle ROM is lower in older adults (e.g. 24.9° in older versus 29.3° in younger adults – a 4.4° difference). A reduced peak plantarflexion angle has also been found in older adults (e.g. 13° versus 17° – a 4° difference).[227] This decrease has been associated with a general weakness of plantarflexor muscles in elders.[218,233] Other studies also found a significantly reduced maximum ankle plantarflexion at both comfortable and fast walking speeds[211] and during late stance[227]; and demonstrate reduced ankle plantarflexion power[226,227,234]; although some argue that this finding may not remain significant when correcting for differences in step length.[227]

Knee extension at mid-stance has been show to increase with age (by about 0.5° per decade) while this angle decreases by 0.5° to 0.8° per decade during swing.[225,227] Elderly people also maintain some knee flexion at terminal swing (e.g. 5.3°)[222] whereas younger adults reach close to full extension (e.g. 0.5°). Prince et al.[221] noted that this flexed angle in elders is associated with a significantly shorter step length, and that it is performed in order to reduce quadriceps demand during loading response. Total knee ROM during the gait cycle is also decreased in the elderly (e.g. 55° in older versus 59° in younger adults – a 4° difference).[227]

In contrast, dynamic hip ROM is increased in older age[222] (e.g. 40° versus 32° – an 8°difference). Oberg et al.,[224] in contrast, failed to demonstrate any significant differences in hip angles between age groups. Along with reduced ankle plantarflexion, Increased hip ROM noted with advancing age has been noted as a distal-to-proximal shift in muscle function to compensate for distal weakness

(called the biomechanical plasticity of ageing gait).[218,232] Reduced peak hip extension and increased pelvic tilt have also been observed; however, these changes may be speed-induced rather than standing postural characteristics.[201,235] The increased anterior pelvic tilt has however also been attributed to the need for placing the hip extensors, which demonstrate an age-associated weakness, at a more favourable length to meet the demand.[221] Reduced pelvis motion in the coronal and transverse planes has also been noted, being about 3° lower in older relative to younger adults.[227]

The gait characteristics specifically associated with falls is less clear, likely because of the fact that collecting data about an unpredictable event, which thus cannot be observed, is a pragmatic challenge. It has however been proposed that the gait characteristics predisposing a person to falls are an exaggeration of the changes noted with ageing.[218] A systematic review[236] found that linear variability of temporal gait parameters (stride, swing and stance time) constitutes the best discriminators between fallers and non-fallers. On the other hand, variability in step width, stride time and speed were best suited to differentiate between older and younger adults.

Gait variability is thought to indicate underlying motor control.[237] Variability may thus quantify age- as well as disease-related changes in the motor control system and in addition serve as a clinically relevant measure of mobility and functional status.[237] Maki et al.[238] furthermore demonstrated the impact of emotional state on fall risk. These authors found that changes in gait parameters (e.g. shorter stride length and slowed speed, and increased double support time) showed an independent association with the *fear* of falling, instead of *actual* falling *per se*. Table 2.3 summarises the changes in TSPs and kinematics proposed in the elderly and fallers, including results from systematic reviews.[236,239,240]

Table 2.3. Gait characteristics commonly proposed to differentiate older from younger adults, and fallers from non-fallers.

	Elderly	Fallers
	Kinematic angles	
Pelvis	• Increased anterior pelvic tilt[221] • Reduced pelvic rotation in coronal and transverse planes during stance[227]	• Increased peak anterior pelvic tilt • Peak anterior pelvic tilt increases with fast walking (not the case in elderly non-fallers)[241]
Hip[a]	• Overall increased ROM[221,239] • Increased flexion at initial contact[239] • Increased peak flexion[239] • Decreased extension during push-off; decreased peak extension[239,242] • Peak extension independent of walking speed[241] • Prolonged adduction during stance phase[227]	• Flexion ROM during GC significantly lower • Decreased flexion angles between mid-stance and late stance phases[243] • Peak extension even lower in elderly fallers compared with non-fallers[241] • Peak hip extension independent from walking speed[241]

	• From SR: small SE of age on hip kinematics; SE ranged from small for hip flexion angle at initial contact, overall hip ROM and peak hip flexion to moderate for peak hip extension[239]	• Decreased abduction angles during mid-stance phase[243] • Increased variability of angles during entire swing phase in all planes[243] • Increased variability of angles during stance phase in coronal plane[243]
Knee[a]	• Gait speed plays critical role on knee kinematics[239] • Overall decreased ROM[221,227] • Increased extension angle at mid-stance[221,227] • Decreased extension during swing phase[221] • Maintenance of slight flexion at end of swing[221] • Increased flexion at initial contact[239] • From SR: current literature does not support a moderate or large difference in knee kinematics[239] • Small overall SE of age on knee kinematics. However, *when accounting for gait speed*, SE for knee ROM was moderate, indicating a larger ROM for older adults[239] • SEs for angle at initial contact, mid-stance peak flexion and peak flexion in swing were not significant[239]	• No statistically significant differences in mean joint angles between fallers and non-fallers[244] • Greater variability of knee joint angles during entire swing phase in all planes[243]
Ankle[a]	• From SE: overall reduced ROM (large SE)[221,239] • Reduced peak plantarflexion angle (moderate SE)[221,239] • Reduced plantarflexion ROM during push-off [242] and reduced plantarflexion angle at toe-off (moderate SE)[239] • Reduced ankle dorsiflexion at initial contact (small yet significant SE)[239]	• Reduced overall dynamic ROM[244] • Dorsiflexion during second phase of double support (A_1 – A_2 power phases/mid-stance to terminal stance) significantly reduced • Plantarflexion at start of swing phase (A_3 – A_2 power phases) significantly lower for fallers[244] • Increased inversion between mid-stance and late stance[243] • Greater variability of angles during entire swing phase in all planes[243] • Greater variability of angles during stance phases in coronal plane[243]
Temporal, spatial, temporophasic and temporospatial parameters		
Gait speed[b,c]	• Reduced gait speed (fallers even more so than non-faller elderly)[240,244,245] • Reduced gait speed also associated with fear of falling[238] • Most consistent finding[218,221]	

Cadence[b,c]	• Contradictory findings • No significant difference compared to younger adults[214,215] • Some findings for differences in variability	• Tendency toward a reduced cadence[240,245,246]
Step and stride time[b,c]	• Longer duration[240]	
Double support time[b,c]	• Longer double support duration (thus delaying the swing phase)[240,244,245] (fallers even more so than non-faller elderly) • Longer double support also associated with fear of falling[238]	
Stride and step length[b,c]	• Shorter length[226,240,242,244,247] (fallers even more so than non-faller elderly) • Reduced length also associated with fear of falling[238]	
Stance time	• Increased in geriatric gait and fallers [222,244,247–249]	
Double support time	• Increased in geriatric gait and fallers[222,250]	
Variability in gait parameters	• Results of a SR[236] demonstrated that the variability in stride time was able to identify both age- and fall-related differences[236] • Linear variability of temporal measures of swing and stance was most capable of distinguishing between fallers and non-fallers[236] • Stride-to-stride variability increases fall risk[238,251,252] - stride-to-stride variability in speed single best independent predictor of falling[238]	

Abbreviations: GC = gait cycle; SE = standardised effect; SR = systematic review.
[a]Note limitations of SR by Boyer et al.[239]: The review did not quantify differences in gait between young, middle-aged and elderly adults and included adults considered as being middle-aged in some cases in the meta-analysis. It is thus difficult to draw conclusions regarding the gait alterations that may be associated with physiological changes brought about by ageing.
[b] Effect size analysis from SR by Mortaza el al.[240] showed that stance time variability, gait speed, stride length and step length were the spatiotemporal parameters that differed most between elderly fallers and non-fallers.
[c]Note limitations of review by Mortaza el al.[240]: The precision of the ES results may be questioned as some included studies and variables lacked mean and SD data - reported effect sizes were thus the average across varying numbers of studies (e.g. only two studies for stride time variability vs. 10 studies for gait speed). Heterogeneity existed between studies regarding methodology, participant selection criteria and definitions for discriminating fallers from non-fallers; and the majority of studies concluded that results regarding the parameters were controversial. Thus, while the review provides a perspective on the current understanding of gait parameters associated with fall risk, results should be interpreted with caution.

2.9. Chapter summary

The evidence regarding the pathophysiology of HIV-1 infection suggests a complex chronic disease in a predominantly middle-aged population. The virus itself, along with various non-communicable comorbidities, HAART, traditional risk factors and synergistic mechanisms to usual ageing all contribute to the motor impairments observed in PLHIV, which in turn contribute to declines in lower limb function. Motor impairments in PLHIV include muscle weakness/dynapenia, motor slowing, postural imbalance and peripheral neuropathy; all of which may influence gait and balance. This might be predictive of adverse outcomes such as falls, which are consistently reported in middle-aged PLHIV and complicated by a high fracture risk in this population. A response to the shift in HIV survivorship was to reconceptualise HIV into a rehabilitation framework, and the importance of prevention (e.g. early screening for functional impairment) is increasingly recognised. Assessments of physical function based on geriatric principles may prove useful tools for HIV clinicians and researchers to help identify those at risk of functional decline. Instrumented analysis of gait and balance in PLHIV may distinguish pathologic patterns, potentially helping to establish associations between pathologies, neuromusculoskeletal contributions, movement patterns and functional consequences. The next chapter will systematically review objective impairments of gait and balance in PLHIV (as evaluated by both clinical functional tests and instrumented analysis), highlighting those potentially related to an increased fall risk.

PART I

CHAPTER 3

Objective impairments of gait and balance in adults living with HIV-1 infection: A systematic review and meta-analysis of observational studies[v]

3.1. Introduction

Both globally and in Sub-Saharan Africa (SSA), the increased survivorship of people living with HIV-1 infection (PLHIV) is paralleled by increasing morbidity. Gait and balance deficits are reported in adults with HIV infection and are associated with reduced quality of life.[6] Gait and postural balance rely on a complex interaction of the motor system, sensory control, and cognitive function. However, due to disease progression and complications related to ongoing inflammation, these systems may be compromised in PLHIV.

Information is building that PLHIV demonstrate gait and balance impairments that can contribute to higher-than-expected fall rates in younger-than-expected cohorts. However, owing to the plethora of observational data, it is difficult to quantify the extent of impairment and to gain insight into which parameters are truly affected and clinically relevant. In elderly populations, several gait and balance parameters have been identified as independent predictors of fall risk, including temporal and spatial, kinetic, kinematic and clinical.[253–256] To the authors' knowledge, no previous systematic review has yet investigated objectively-measured impairments of gait and balance in PLHIV.

The aims of the systematic review undertaken during Phase I of this project were therefore to:

i. synthesise the evidence of objective impairments of gait and balance associated with HIV-1 infection, emphasising those that could contribute to increased fall risk;
ii. describe the evidence in relation to disease severity, treatment association, task difficulty, and peripheral neuropathy.

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[v] *This chapter was published in a peer-reviewed journal as: Berner K, Morris L, Baumeister J, Louw Q. Objective impairments of gait and balance in adults living with HIV-1 infection: a systematic review and meta-analysis of observational studies. BMC Musculoskelet Disord 2017;18(1):325 (Appendix N).*

3.2. Methods

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[257]

3.2.1. Criteria for considering studies for this review

Cohort, case control and cross-sectional studies published in English as peer-reviewed journal articles were considered. Studies were included if they aimed to assess instrumented or non-instrumented objective parameters of gait and/or balance in adults (18 to 65 years of age) with HIV-1 infection, irrespective of gender. Given the expectation that there would be a paucity of information, studies with and without comparison groups were considered. Quantitative gait outcomes were included, but were not limited to, kinematics, kinetics, spatiotemporal measures or clinical tests. Quantitative balance outcomes included, but were not limited to, biomechanical parameters such as centre of pressure (COP) measures, and temporal measures via clinical tests. Studies were excluded if participants' age exceeded 65 years, as the prevalence of locomotor impairments is known to increase in older age even in healthy populations.[258] Studies aiming to assess HIV-Associated Neurocognitive Disorder using a neuropsychological test battery were also excluded, regardless of the use of a gross motor component, in an attempt to focus on studies with the primary aim of objectively assessing and describing gait or balance in PLHIV.

3.2.2. Search methods for identification of studies

3.2.2.1. Information sources

Six computerised bibliographic databases were searched, namely PubMed, Science Direct, EBSCOhost (CINAHL, MEDLINE, Africa-Wide Information), Scopus, ProQuest Medical Library and Google Scholar. Following a preliminary search of PubMed, a comprehensive search strategy, including all relevant key word/terms and medical subject headings (MeSH) was developed and adapted for use in subsequent searching of the remaining databases. Search terms included: *(HIV-1 OR HIV Infection*) AND (motor function OR biomechanical phenomena OR gait OR postural balance OR locomotor function).* The search was restricted to papers published from inception of the database to April 2016. Reference lists of all identified documents were hand-searched to identify additional relevant evidence. In the event of missing data, an attempt was made to contact the authors.

3.2.2.2. Study selection

Titles and abstracts of all initial hits were screened by one reviewer (the PhD candidate, KB). When necessary, consultation with a second reviewer (the promotor, QL) was pursued. All potential full texts were subsequently screened by these two reviewers, and eligibility criteria were applied independently. Any discrepancies regarding eligibility were discussed between reviewers to reach consensus.

3.2.3. Data collection and analysis

3.2.3.1. Methodological quality appraisal

One reviewer (the PhD candidate) appraised the methodological quality of each included study using the National Institutes of Health (NIH) Quality Assessment tool for Observational Cohort and Cross Sectional Studies.[259] The tool is designed to aid appraisal of internal validity (potential risk of selection-, information-, or measurement bias, or confounding) of cross-sectional and cohort studies and was therefore appropriate for this review. It comprises 14 criteria. All criteria can be answered as "yes", "no", "cannot determine", "not applicable" or "not reported". All responses other than "yes" indicate risk of bias. Inherent to the design, cross-sectional studies automatically score "not applicable" on criteria 6, 7, 10 and 13. After all 17 articles were scored by the first reviewer, two of these were randomly selected for audit and independently scored by a second reviewer (the co-promotor, LM). The scores assigned by each reviewer were compared by specifically discussing those criteria with discrepant scores. Consistent discrepancies were noted specifically for criteria 6, 10 and 13 for both studies – which were resolved after agreeing that these criteria should be scored as “not applicable” as per the instrument’s instructions. Resultant total scores were similar; thus, it was not deemed necessary for the second reviewer to score the remaining 15 articles as well. Each criterion was weighted equally in the overall grading, and studies were not excluded based on quality score, due to the expected dearth of information.

3.2.3.2. Data extraction

Data extracted from each study were summarised using a customised Excel spreadsheet, based on Cochrane forms. Information about sample demographics as well as the study aims, study design, known confounders to gait and balance, descriptors of HIV-disease, gait or balance analysis tool or test used, specific objective gait or balance outcomes, dose-response evidence, associations with treatment, associations with disease severity, association of peripheral neuropathy, findings and limitations of each study were extracted. Principle summary measures were means and standard deviations (SD).

3.2.3.3. Data analysis or synthesis

Narrative description of data was done using text summaries or tables as appropriate. For outcomes that were reported in at least two studies, a meta-analysis was conducted in Revman version 5.2, provided that homogeneity in the outcomes and samples existed regarding units of measurement, test conditions, gender and disease severity. Mean differences and 95% confidence intervals (CI) were calculated via a random effects model, provided that means and SD were reported; these were presented graphically as forest plots. Symptomatic (presenting with various symptoms of chronic HIV disease) and asymptomatic (asymptomatic HIV infection/clinically latent phase of HIV) subgroups of PLHIV were analysed.

3.3. Results

3.3.1. Study selection

The initial search in March 2016 produced 799 total hits (Figure 3.1). After removing duplicates and applying eligibility criteria, 93 potential titles remained. Thirty studies were subsequently excluded upon reading the abstracts. The main reasons for exclusion were that the outcome measures were not relevant to the review question, participants were not within the specified age range, and study design was inappropriate. Following full text review, the number of studies for inclusion was reduced to 17. Primary reasons for exclusion were inability to obtain full text, ineligible participants, no raw data and outcomes that were not relevant to the review question.

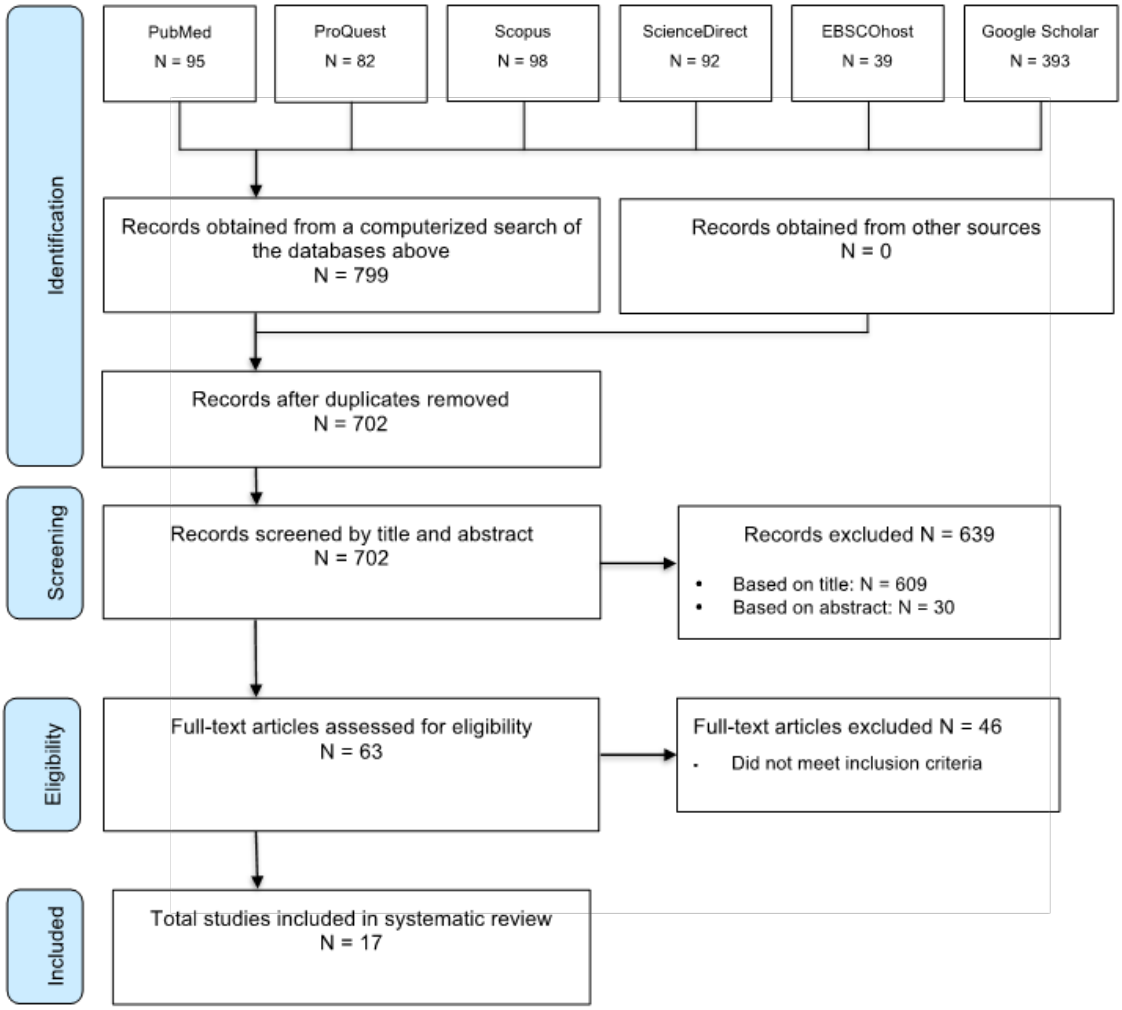


Figure 3.1. PRISMA flow diagram of literature search and selection process.

3.3.2. Study characteristics

3.3.2.1. Critical appraisal of study quality

Table 3.1 presents the methodological quality appraisal scores of the included studies, which ranged from fair to poor. A mean score of 40.34% was obtained, ranging from 7.14% (lowest internal validity amongst the included studies) to 57.14% (strongest internal validity amongst the included studies).

3.3.2.2. Study sample description

Participant numbers varied from 19 to 447. Six studies did not include a control group.[2,3,55,59,121,260] Mean ages ranged from 28.0 to 54.7 years. Two studies included males only.[121,261] Only one study[51] was conducted in Sub-Saharan Africa. Table 3.2 summarises the sample characteristics of all participants, while HIV-specific sample characteristics are presented in Table 3.3.

Table 3.1 Methodological quality appraisal of included studies.

		Trenkwalder 1992[114]	Arendt 1994[115]	Beckley 1998[262]	Bauer 2005[113]	Dellepiane 2005[263]	Simmonds 2005[49]	Scott 2007[121]	Richert 2011[2]	Bauer 2011[32]	Sullivan 2011[33]	Erlandson 2012a[59]	Erlandson 2012b[55]	Cohen 2012[264]	Beans 2013[261]	Mbada 2013[51]	Richert 2014[3]	Erlandson 2014[260]
1	Research question/objective clearly stated?	N	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y
2	Study population clearly specified and defined?	N	N	N	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
3	Participation rate of eligible persons at least 50%?	CD	CD	CD	CD	CD	CD	CD	N	CD	CD	Y	Y	Y	Y	CD	N	CD
4	All subjects recruited from similar populations? Eligibility criteria pre-specified and applied uniformly?	NR	N	N	Y	NR	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
5	Justification of sample size?	N	N	N	Y	N	N	N	N	N	N	N	N	N	N	N	N	N
6	Exposure(s) measured prior to outcome(s)?*	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Y	NA
7	Sufficient timeframe to see an association between exposure and outcome?*	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Y	NA
8	Different levels of the exposure measured, as related to the outcome?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
9	Exposure measures clearly defined, valid, reliable, and implemented consistently?	NR	Y	Y	Y	NR	Y	Y	Y	Y	Y	Y	Y	Y	NR	Y	Y	Y

10	Exposure(s) assessed more than once over time?*	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	CD	NA
11	Outcome measures clearly defined, valid, reliable, and implemented consistently?	CD	NR	NR	NR	CD	Y	Y	NR	Y	NR	N	N	N	Y	Y	NR	CD
12	Outcome assessors blinded to exposure status?	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
13	Loss to follow-up after baseline ≤ 20%?*	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	N	NA
14	Key potential confounders measured and statistically adjusted for?	N	N	N	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Total CAT score /14	1	3	3	7	2	6	7	6	6	6	7	7	7	7	7	8	6
	Total CAT %	7.14	21.43	21.43	50	14.29	42.86	50	42.86	42.86	42.86	50	50	50	50	50	57.14	42.86

Abbreviations: CD = cannot determine; NA = not applicable; NR = not reported.
**Cross-sectional analyses provide weaker evidence than cohort studies regarding a potential causal relationship between exposures and outcomes. For cross-sectional analyses, the answer to Questions 6, 7, 10 & 13 should be "Not applicable". All studies were cross-sectional, except for Richert 2014[3] (prospective longitudinal cohort).*

Table 3.2. Sample characteristics: all participants.

Study ID	Country, setting	Serostatus & Sample size (N)	Gender (%)	Age (years) (SD)	BMI (kg/m^2) (SD)	Edu-cation (years) (SD)	Recreational drug use / Alcohol consumption / smoking (N)	Depression / PN / Other co-morbidities
Trenkwalder 1992[114]	Germany, NR	HIV+ 50	M 96 F 4	42.5 (9.3)	NR	NR	4 / NR / NR	NR / Yes / Various neurological deficits
		HIV- 50	NR	37.5 (11.0)	NR	NR	NR / NR / NR	NR / NR / Healthy
Arendt 1994[115]	Germany, NR	HIV+ 46	M 74 F 26	ASX: 36.33 (9.18) SX: 38.8 (8.38)	NR	NR	0 / 0 / NR	NR / No / HIV type-1-related encephalopathy (n=10)
		HIV- 38	M 53 F 47	37.7 (10.21)	NR	NR	NR / NR / NR	NR / NR / Healthy
Beckley 1998[262]	USA, NR	HIV+ 9	M 89 F 11	38.9 (10.7)	NR	NR	0 / 0 / NR	NR / No / PGL (n = 2); Opportunistic infection (n = 3)
		HIV- 10*	M 50 F 50	34.3 (7.8)	NR	NR	NR / NR / NR	NR / No / Healthy
Bauer 2005[113]	USA, outpatient infectious disease clinics	HIV+ 90	M 39 F 61	NRx: 40 (7.2) NNRTI: 40 (5.9) PI: 39 (6.4)	NR	NRx: 11.5 (1.6); NNRTI: 11.6 (1.7); PI: 12.1 (2.6)	Large % Hx of drug abuse / NRx: 39.3%; NNRTI: 40%; PI: 35.1% / NR	NRx: 42.9%, NNRTI: 28%, PI: 35.1% / NR / Exclusion criteria eliminated major psychiatric-, medical- & neurological disorders
		HIV- 78	M 47.4 F 52.6	38 (7.1)	NR	12.6 (2.2)	Large % Hx of drug abuse / 16.7% / NR	17.9% / NR / Healthy

Simmonds 2005[49]	USA, out-patient AIDS facility	HIV+ 100	M 78 F 22	40.70 (7.49)	NR	NR	NR / NR / NR	NR / No / Exclusion criteria eliminated major medical & neurological disorders
		HIV- 105*	M 37 F 63	44.9 (14.7)	NR	NR	NR / NR / NR	NR / No / Healthy
Dellepiane 2005[263]	Italy, NR	HIV+ 30	M 40 F 60	ASX: 28 (NR) AIDS: 32.8 (NR)	NR	NR	NR / NR / NR	NR / NR / Alcoholic cirrhosis (n=1); no neurological or oto-neurological symptoms
		HIV- 55	M 64 F 36	35 (NR)	NR	NR	NR / NR / NR	NR / NR / Healthy
Scott 2007[121]	USA, HIV clinic	HIV+ 27	M 100	48.7 (6.5)	24.2 (4.1)	NR	NR / NR / NR	NR / NR / Exclusion criteria eliminated major medical & neurological disorders
Richert 2011[2]	France, HIV clinics	HIV+ 324	M 80 F 20	#47.6 (41.8, 53.9)	#22.5 (20.6, 24.6)	NR	NR / NR / NR	NR / 14% / Hepatitis B: 7%, Hepatitis C: 19%
Bauer 2011[32]	USA, outpatient infectious disease clinics	HIV+ 121	M 58 F 42	BMI<21: 39.4 (1.0); BMI 21-29: 40.9 (0.8); BMI>29: 37.6 (1.2)	<21(n = 35); 21-29 (n = 61); >29(n=25)	NR	No differences between groups / No differences between groups / NR	Significant differences ($p < 0.05$) / NR / Exclusion criteria eliminated major psychiatric-, medical- & neurological disorders
		HIV- 86	M 49 F 51	BMI<21: 38.5 (1.3); BMI 21-29: 38.0 (1.1); BMI>29: 36.6 (1.0)	<21(n = 2); 21-29 (n = 30); >29 (n=35)	NR	No differences between groups / No differences between groups / NR	Significant differences ($p < 0.05$) / NR / Healthy

Sullivan 2011[33]	USA, HIV clinics, local community	HIV+ 40	M 70 F 30	41 (NR)	M 25.4 (3.34); F 26 (3.16)	M 14.1 (3.05); F 13.8 (2.67)	NR / No differences between groups / M 43%, F 20%	BDI: M 10.5 (8.33); F 12.8 (9.26) / M 26%, F 17% / NR
		HIV- 83	M 48 F 52	44 (NR)	M 26.9 (4.83); F 24.7 (4.49)	M 15.9 (2.27); F 15.3 (2.00)	NR / No differences between groups / M 10%, F 0%	BDI: M 2.08 (2.33), F 2.9 (3.08) / NR / Without medical or psychiatric conditions
Erlandson 2012a[59]	USA, Infectious Diseases Group Practice clinic	HIV+ 359	M 85 F 15	#50.8 (47.7, 55.7)	NR	NR	IDU (<1%), Cocaine (<1%), Marijuana (23%) / >7 drinks/wk (4%) / Current: 34%	NR / NR / NR
Erlandson 2012b[55]	USA, Infectious Diseases Group Practice clinic	HIV+ 359	M 85 F 15	52 (0.3)	NR	NR	Current IDU (<1%) / >7 drinks/wk: Non-fallers (4%), Single fallers (7%), Re-fallers (2%) / Non-fallers (30%), Single-fallers (42%), Re-fallers (47%)	NR / NR / 30% reported ≥1 falls during the past year (of those, 61% were recurrent fallers)
Cohen 2012[264]	USA, multiple clinical subsites	HIV+ 247	M 51 F 49	48.9 (8.9)	NR	NR	NR / No / NR	NR / NR / Exclusion criteria eliminated spinal injury, vestibular impairment, use of narcotics, antihistamines or sedatives within 48 hours of testing
		HIV- 200	M 84 F 16	54.2 (11.2)	NR	NR	NR / No / NR	NR / NR / NR
Beans 2013[261]	USA, Baltimore VA	HIV+ 45	M 100	54.4 (6.3)	<25 (51.1%)	NR	NR / NR / 69.0%	NR / NR / Diabetes 26.7%, Hepatitis C

	Medical Center				≥25 (48.9%)			71.1%, Hypertension 68.9%, Chronic Pulmonary Disease 20%, Dyslipidemia 36.4%, Anemia 24.4%
		HIV- 27	M 100	54.7 (6.2)	<25 (32.4%) ≥25 (67.6%)	NR	NR / NR / 56.8%	NR / NR / Diabetes 18.9%, Hepatitis C 55.6%, Hypertension 73%, Chronic Pulmonary Disease 29.7%, Dyslipidemia 25.8%, Anemia 37.8%
Mbada 2013[51]	Nigeria, Virology Research Clinic	HIV+ 37 HIV- 37	M 40.5 F 59.5 M 40.5 F 59.5	35.68 (7.71) 35.73 (7.88)	22.77 (4.17) 24.31 (4.24)	NR NR	NR / NR / NR NR / NR / NR	NR / NR / NR NR / NR / Healthy
Richert 2014[3]	France, HIV clinics	HIV+ 178	M 81 F 19	#48 (43, 56)	#22.2 (20.5, 24.5)	NR	Prior IDU (14%) / NR / NR	NR / NR / Cerebral CDC stage C condition: 3%, Hepatitis B: 7%, Hepatitis C: 20%
Erlandson 2014[260]	USA, Infectious Diseases clinic	HIV+ 359	M 85 F 15	52 (5.2)	26.4 (6.0)	NR	Current IDU (<1%) / NR / NR	NR / NR / NR

Abbreviations: AIDS = Acquired Human Immunodeficiency Syndrome; ART = antiretroviral therapy; ASX = asymptomatic; BDI = Beck Depression Inventory; BMI = Body Mass Index, CDC = Centre for Disease Control; DAST-10 = Drug Abuse Screening Test; F = female; HAART = highly active antiretroviral therapy; HIV = human immunodeficiency virus; Hx = history; IDU = intravenous drug use; M = male; MAST = Michigan Alcoholism Screening Test; MDD = Major Depressive Disorder; N = number of participants,; NA = not applicable; NNRTI = non-nucleoside reverse transcriptase inhibitor; NR = not reported; NRTI = nucleoside reverse transcriptase inhibitor; NRx = no treatment; PGL = Persistent generalized lymphadenopathy; PI = protease inhibitor; PN = peripheral neuropathy; SD = Standard Deviation; SX = symptomatic; USA = United States of America; WR = Walter Reed stages.
**Retrospective control group of healthy volunteers from previous study. #Median (IQR).*

Table 3.3. Sample characteristics: people living with HIV-1 infection (PLHIV).

Study ID	Disease staging	CD4 cell count, cells/mm^3 (SD)	Viral load (SD)	Treatment
Trenkwalder 1992[114]	WR I-II (N=17); WR III-V (N=19); WR VI (N=14)	NR	NR	NR
Arendt 1994[115]	CDC II (N=12); CDC III (N=12); CDC IV C1 (N=5); CDC IV C2 (N=5); CDC IV D (N=2); CDC IV B (N=10)	NR	NR	NR
Beckley 1998[262]	ASX (N=2); CDC Stage A (N=2); CDC Stage B (N=2); CDC Stage C (N=3)	Range 65 - 701; 5 participants had AIDS-defining CD4 counts (<200)	NR	Most were on zidovudine maintenance therapy
Bauer 2005[30]	NR	NRx: 351(282); NNRTI: 457(375); PI: 320(200)	*HIV burden x 1000 copies/ml:* NRx: 93.8 (163); NNRTI: 35.5 (102); PI: 20.1 (48.2)	NRx: N=28; NNRTI: N=25; PI: N=37
Simmonds 2005[49]	*Based on CD4 count* ASX (CD4>200) (N=52); AIDS (CD4<200) (N=48)	Range 189.83 (183.27) - 386.36 (302.39)	*Virions:* ASX 33 545.25; AIDS 193 401.00	NR
Dellepiane 2005[263]	*CDC classification* ASX (N=15); AIDS (group IV) (N=15)	NR	NR	NR
Scott 2007[121]	NR	408 (293)	*log copies/ml* 2.18 (0.94)	All were on a NRTI-based regimen, with 82% receiving a PI as a third agent
Richert 2011[2]	CDC category C: 23%	#520 (348, 709)	<500 copies/ml: 83%	89%
Bauer 2011[32]	NR	BMI <21: 280 (52); BMI 21-29: 422 (40); BMI>29: 361 (64)	*Log10 viral load* BMI <21: 3.06 (0.34); BMI 21-29: 2.19 (0.26); BMI>29: 2.08 (0.39)	*% no ART/NNRTI-based ART/ PI-based ART:* BMI <21: 38.2/26.5/35.3; BMI 21-29: 31.7/26.7/ 41.7; BMI>29: 37.0/18.5/44.4
Sullivan 2011[33]	NR	M 537.4 (258.97); F 583.4 (103.55)	M 13597.6 (4654.88); F	HAART: N=25; Non-HAART: N=6; NRx: N=9

			4609.7 (3226.36)	
Erlandson 2012a[59]	NR	#551 (361, 768)	Detectable (≥48 copies/mL): 5%	NR
Erlandson 2012b[55]	NR	594 (16)	95% had plasma HIV-1 RNA < limits of detection	Any didanosine: Non-fallers: 57 (23); Single fallers: 10 (23); Recurrent fallers: 24 (36) Any stavudine: Non-fallers: 93 (37) Single fallers: 22 (51); Recurrent fallers: 33 (50) Efavirenz: Non-fallers: 86 (34); Single fallers: 10 (23); Recurrent fallers: 22 (33)
Cohen 2012[264]	NR	556.4 (284)	*Log_{10} HIV RNA:* #3.50 (2.68, 4.42)	HAART: 76.9%
Beans 2013[261]	NR	#445 (265, 531)	Non-detectable (<400 copies/ml): 91%	Majority were receiving cART
Mbada 2013[51]	All: Clinical stage I of HIV/AIDS (ASX HIV infection, with PGL)	NR	NR	100% HAART
Richert 2014[3]	CDC stage C 24%	#506 (340, 715)	HIV RNA level <500 copies/ml: 84%	89% on ART
Erlandson 2014[260]	NR	594 (303)	HIV-1 RNA < limits of detection: 95%	All participants taking effective cART

Abbreviations: AIDS = acquired immunodeficiency syndrome; ART = antiretroviral therapy; ASX = asymptomatic; BMI = Body Mass Index; cART = combination antiretroviral therapy; CDC = Centre for Disease Control; F = female; HAART = highly active antiretroviral therapy; HIV = human immunodeficiency virus; IQR = interquartile range; M = male; N = number of participants; NA = not applicable; NNRTI = non-nucleoside reverse transcriptase inhibitor; NR= not reported; NRTI = nucleoside reverse transcriptase inhibitors; NRx = no treatment; PGL = Persistent generalized lymphadenopathy; PI = protease inhibitor; PLHIV = people living with HIV; SD = standard deviation; SX = symptomatic; WR = Walter Reed staging. # Median (IQR).

3.3.2.3. Study design, aims and outcomes

Sixteen studies were cross-sectional, and one was a prospective cohort.[3] Study aims varied (Table 3.4), but all included objective measurement of balance and/or gait as part of the primary aim. Balance was assessed using both clinical and instrumented tests. All studies used timed clinical tests for assessing gait. No studies assessed gait kinetics or kinematics. Outcomes varied substantially. Table 3.5 (balance) and Table 3.6 (gait) present the outcomes assessed per study. Summaries of the results for individual outcomes are presented briefly in Table 3.7 (balance) and Table 3.8 (gait), and presented in more detail as additional files to the published document (see Addendum N).

Table 3.4. Aims of included studies.

Study ID	Design	Aim
Trenkwalder 1992[114]	Cross-sectional	To measure postural performance quantitively in PLHIV (in different disease stages) versus seronegative controls, using a force plate.
Arendt 1994[115]	Cross-sectional	To determine if stance control is impaired in early versus late HIV infection, using a force plate, and to compare results with the COG patterns in pyramidal or extrapyramidal disease.
Beckley 1998[262]	Cross-sectional	To evaluate postural reflexes with EMG in PLHIV without obvious neurological disease, in order to determine whether postural reflexes are early markers of CNS involvement.
Bauer 2005[30]	Cross-sectional	To assess sensorimotor function in PLHIV and seronegative controls.
Simmonds 2005[49]	Cross-sectional	To characterize physical performance in PLHIV, and to examine group differences by pain and fatigue.
Dellepiane 2005[263]	Cross-sectional	To investigate whether posturography can detect the presence of possible disorders of the vestibulo-spinal reflex.
Scott 2007[121]	Cross-sectional	To determine the extent of neuromuscular activation of selected lower limb muscles of male PLHIV receiving ART, and its relationship to performance in clinical functional tests.
Richert 2011[2]	Cross-sectional	To provide standardized assessments of locomotor function in PLHIV, focusing on lower limb muscle performance and balance, and on potential determinants of functional impairment.
Bauer 2011[32]	Cross-sectional	To compare balance and gait in participants who differ in BMI and the presence or absence of HIV/AIDS.
Sullivan 2011[33]	Cross-sectional	To investigate whether infratentorial brain volume would be marked by regional tissue shrinkage in PLHIV versus seronegative controls, and whether tissue deficits would be related to impairment in postural stability or

		psychomotor speed, using structural MRI and quantitative tests of postural stability, finger movement, psychomotor speed and dexterity.
Erlandson 2012a[59]	Cross-sectional	To compare the FFP, SPPB, and 400-m walk in PLHIV.
Erlandson 2012b[55]	Cross-sectional	To determine fall-rate and -risk factors among PLHIV by correlating fall history, medical diagnoses, and functional tests.
Cohen 2012[264]	Cross-sectional	To determine whether PLHIV on HAART had an increased prevalence of vestibular disorders versus seronegative controls, using standard screening tests of vestibular and balance function.
Beans 2013[261]	Cross-sectional	To compare locomotor function in male PLHIV versus seronegative controls, and test the association with aerobic exercise capacity.
Mbada 2013[51]	Cross-sectional	To compare HRQOL and a performance-based measure of functional capacity between a homogenous sample of clinical stage I PLHIV versus seronegative controls.
Richert 2014[3]	Prospective cohort	To prospectively assess the changes in locomotor function in PLHIV over time and to evaluate the determinants of variations in lower limb muscle performance.
Erlandson 2014[260]	Cross-sectional	To assess the impact of physical function impairments on HRQOL in PLHIV using ART.

Abbreviations: ART = antiretroviral therapy; BMI = body mass index; CNS = central nervous system; COG = centre of gravity; EMG = electromyography; FFP = Fried's Frailty Phenotype; HRQOL = health-related quality of life; PLHIV = people living with HIV; SPPB = Short Physical Performance Battery.

Table 3.5. Studies assessing balance outcomes.

		Trenkwalder 1992[114]	Arendt 1994[115]	Beckley 1998[262]	Bauer 2005[30]	Dellepiane 2005[263]	Simmonds 2005[49]	Richert 2011[2]	Bauer 2011[32]	Sullivan 2011[33]	Cohen 2012[264]	Erlandson 2012a[59]	Erlandson 2012b[55]	Richert 2014[3]	Erlandson 2014[260]	**Total studies assessing outcome**
Balance outcome	Mean sway path (m/min)	X														**1**
	Sway velocity (m/sec)		X													**1**
	Sway area (μVxs)		X			X										**2[a]**
	AP					X										**1**
	LAT					X										**1**
	AP/LAT quotient		X			X										**2[b]**
	Romberg ratio of sway velocity; RW		X			X										**2[a]**
	Romberg area of sway; RA					X										**1**
	Way					X										**1**
	SOT sway strategy score								X							**1**
	SOT EQ				X											**1**
	SOT number of falls; time before fall				X											**1**
	FBOS; LOS				X				X							**2[c]**
	Latencies of postural reflexes (ms)		X	X		X										**3[a]**
	Duration of postural reflexes					X										**1**
	Amplitude of postural reflexes					X										**1**
	Area of single EMG potential					X										**1**
	Normalized amplitude of ML-response			X												**1**
	Standardized LL Z-scores			X												**1**
	Romberg ECF (sec)										X					**1**
	Tandem stance (sec)									X						**1**
	Single leg stance time (sec)							X	X	X				X		**4[d]**

Berg balance score							X								**1**
TUG time (sec)							X						X		**2[e]**
5STS time (sec)							X	X					X		**3[f]**
5STS pace (rises/sec)														X	**1**
360° turn time								X							**1**
Walk heel-to-toe (number of steps)									X						**1**
Forward reach distance (cm)						X	X								**2[g]**

Abbreviations: 5STS = 5-Times Sit-To-Stand Test; AP = average velocity in an anterior-posterior direction; cm = centimeters; ECF = eyes-closed-on-foam; EMG = electromyography; EQ = equilibrium quotient; FBOS = functional base of support; LAT = average velocity in a medial-lateral direction; LL = long loop; LOS = limits of stability; m = metres; min = minute; ML = medium loop; ms = millisecond; RA = Romberg area of sway; RW = Romberg ratio of sway velocity; sec = second; SOT = Sensory Organisation Test; TUG = Timed-Up-And-Go Test.

[a]Meta-analysis performed; [b]Meta-analysis not done as Arendt 1994 does not report SD values; [c]Meta-analysis not done as Bauer 2005 does not report values for control group; [d]Meta-analysis not done due to heterogeneity in methodologies: Richert 2011 uses established normative values as comparison; Sullivan 2011 uses max time of 60 sec, Richert 2014 has no comparison values; [e]Meta-analysis not done as Richert 2014 has no comparison group; [f]Meta-analysis not done as Richert 2011 & 2014 has no comparison groups; [g]Meta-analysis not done as Richert 2011 uses established normative values as comparison.

Table 3.6. Studies assessing gait outcomes.

		Bauer 2005[30]	Simmonds 2005[49]	Scott 2007[121]	Richert 2011[2]	Bauer 2011[32]	Erlandson 2012a[59]	Erlandson 2012b[55]	Beans 2013[261]	Mbada 2013[51]	Richert 2014[3]	Erlandson 2014[260]	Total studies assessing outcome
Gait outcomes	Gait speed (m/sec), preferred and/or fast					X	X	X			X	X	**5[a]**
	Timed gait (sec)	X	X						X				**3[b]**
	Cadence (time in sec for 5 steps), fast and preferred	X				X							**2**
	Gait initiation time (sec), fast and preferred					X							**1**
	6MWD		X	X	X				X	X	X		**6[c]**

Abbreviations: 6MWD = 6-Minute Walk Distance; m = metre; sec = second.
[a]Meta-analysis not possible as Bauer 2005 did not report mean results for gait speed and Richert 2014 included no comparison group or norm values. [b]Meta-analysis not possible as Bauer 2005 did not report mean for gait speed and Erlandson 2012a, 2012b & 2014 included no comparison groups or norm values. [c]Only 4 out of 6 studies included in meta-analysis, as Richert 2011 & 2014 included no comparison groups or norm values (note heterogeneity between samples of the 4 studies included meta-analysis). [d]Meta-analysis not possible, as Bauer 2005 did not report mean results for cadence or gait initiation time.

Table 3.7. Summary of objective balance outcomes and results.

Study ID	Results	Method of measurement	Outcomes assessed
Trenkwalder 1992[114]	a, b	4 conditions on force plate: Bilat stance EO + stable; Bilat stance EC + stable; Bilat stance EO + foam; Bilat stance EC + foam.	Mean sway path (m/min): EO & EC + foam[b] (all PLHIV except WR I-II) / EC + stable or foam[b] (all PLHIV) / All other conditions[a]
Arendt 1994[115]	a, b	2 conditions on force plate: Bilateral stance EO; Bilateral stance EC.	Sway velocity (m/sec)[b] / AP/LAT quotient[a]
Beckley 1998[262]	a, b	Leg reflexes elicited in participants while standing upright on movable force plate - surface EMG recordings obtained from left tibialis anterior and medial gastrocnemius	Onset latencies (SL, ML and LL) (ms) / Normalised amplitude of ML[a] / LL-amplitude scaling (predictable[a]; unpredictable[b])
Bauer 2005[30]	a, b	1) SOT, 3 conditions: EO, EC, inaccurate visual input 2) Forward/backward lean tests 3) (Single-leg stance test)	1) SOT, for each condition: EQ (EO[a], EC[b], inaccurate[a]) / Number of falls[a] / Time before a fall (seconds)[a] 2) FBOS (Lean amplitude/foot length[b] 3) (Single Leg Stance time (s) - results not presented)
Simmonds 2005[49]	a	Loaded forward reach Unloaded forward reach	Distance reached (cm)[a]
Richert 2011[2]	a, c	1) BBS 2) TUG test 3) FR test 4) SLS, EC 5) 5STS	1) Berg score[a] 2) TUG time (sec)[a] 3) Reach distance (cm)[a] 4) SLS time (sec)[c] 5) 5STS time (sec)[c]
Dellepiane 2005[263]	a, b	1) Static posturography: Romberg's position on force plate; EO & EC 2) Dynamic posturography: EO & EC; leg reflexes elicited via sudden tilts of moveable force plate, EMG recorded	1) Static: Way (EO & EC, SX[b]), Area, AP (ASX in EC[b], SX in EO[b] & EC[b]), LAT (SX in EC[b]), AP/LAT[a], RW, RA[b] 2) Dynamic (SL, ML and LL): Latency (SL: EO & EC, all HIV groups[b]) (ML: EO, SX, both legs[b]; EO, ASX, left leg[b]; EC, all groups[a]) (LL: EC, SX[b]; EC, ASX[a]) / Duration (SL: EO, all PLHIV[a]; EC, SX, left leg[b]) (ML: EO, all PLHIV[a]; EC, all PLHIV, bilat[b]) (LL, EC, all PLHIV[b]) / Amplitude[a] /Area of single EMG[a]

Bauer 2011[32]	a, b	1) SOT, 3 conditions: EO, EC, inaccurate visual input 2) Forward/backward lean tests 3) SLS test 4) 360-degree turn test 5) 5STS test	1) SOT: Dependent variables calculated for each condition were: EQ (EC[b], inaccurate input[b]) Sway strategy score (EC[b]) 2) LOS (lean amplitude/foot length)[b] 3) SLST time (seconds) (only obese PLHIV, non-preferred leg[b]) 4) 360 deg turn time (seconds) (only obese PLHIV[b]) 5) 5STS time (seconds)[a]
Sullivan 2011[33]	a, b	Walk-a-Line Battery. Conditions: Stand Heel-to-Toe; Walk Heel-to-Toe; and SLS.	1) Stand Heel-to-Toe time (seconds)[a] 2) SLS time (seconds) (non-preferred leg[b]) 3) Walk-Heel-to-Toe - number of steps out of 10 (EC[b])
Cohen 2012[264]	c	Romberg tests on stable and on foam, 4 conditions: EO + stable, EC + stable, EO + foam, EC + foam.	Romberg time, EC + foam (seconds)[c]
Erlandson 2012a[59]	c	Tandem stand and 5STS as part of SPPB	5STS time (part of SPPB score) † / Tandem stance time (part of SPPB score)[c]
Erlandson 2012b[55]	c	Tandem stand and 5STS as part of SPPB	5STS time (part of SPPB score)[c] / Tandem stance time (part of SPPB score)[c]
Richert 2014[3]	c	1) 5STS test 2) TUG test 3) SLS test	1) 5STS time (seconds)[c] 2) TUG time (seconds)[c] 3) SLS time (seconds)[c]
Erlandson 2014[260]	c	5STS	5STS pace (rises/second)[c]

Abbreviations: 5STS = 5-Times-Sit-To-Stand; AP = Average velocity in anterior-posterior direction; ASX = asymptomatic; BBS = Berg Balance Scale; Bilat = bilateral; COP = centre of pressure; deg = degree; EC = eyes closed; EMG = electromyography; EO = eyes open; EQ = equilibrium quotient; FBOS = functional base of support; FR = functional reach; LAT = average velocity in medial-lateral direction; LL = long loop; LOS = limits of stability; ML = medium loop; PLHIV = people living with HIV; RW = Romberg index reported to way = ratio of way with EO & EC; RA = Romberg index reported to area = ratio of area with EO & EC; SL = short loop; SLS = single leg stance; SOT = Sensory Organisation Test; SX = symptomatic; TUG = Timed-Up-And-Go. Outcomes included in meta-analyses are not included in this table.

[a] no significant difference between PLHIV and controls. [b] PLHIV significantly impaired compared to controls or normative reference values. [c] No comparison provided/impairment quantified by reporting proportion of PLHIV with deficits.

Table 3.8. Summary of objective gait outcomes and results.

Study ID	Results	Method of assessment	Spatiotemporal outcome
Bauer 2005[30]	a	8-m walk (preferred and fast)	Gait speed: time (sec) to cover distance[a] Cadence (time in sec for 5 steps)[a]
Simmonds 2005[49]	b	50-foot (15.24-m) walk (preferred and fast)	Gait speed: time (sec) to cover distance[b]
Scott 2007[121]	b	6MWD	Distance covered (m) in 6 min[b]
Richert 2011[2]	c	6MWD	Distance covered (m) in 6 min[c]
Bauer 2011[32]	b	8-m walk (preferred and fast)	Preferred[b] and fast gait initiation time (sec) Fast[b] and preferred gait speed (m/sec) Fast and preferred cadence (time in sec for 5 steps)
Erlandson 2012a[59]	c	4-m walk as part of SPPB 400-m walk (fast)	Only presented as part of SPPB score Gait speed (m/sec)[c]
Erlandson 2012b[55]	c	1) 4-m walk as part of SPPB 2) 400-m walk (fast)	1) Only presented as part of SPPB score 2) Gait speed (m/sec)[c]
Beans 2013[261]	a, d	1) 6MWD 2) 400-meter long distance corridor walk	1) Distance covered (m) in 6min[a] 2) Gait speed: time (sec) to cover distance[d]
Richert 2014[3]	b	1) 6MWD 2) 10-m walk	1) Distance covered (m) in 6min[b] 2) Gait speed (m/sec)
Erlandson 2014[260]	c	400-m walk (fast pace)	Gait speed (m/sec)[c]

Abbreviations: 6MWD = Six-minute walk distance; m = metres; min = minutes; sec = seconds; SPPB = short physical performance battery.
Outcomes included in meta-analyses are not included in this table.
[a] No significant difference between PLHIV and controls. [b] PLHIV significantly impaired compared to controls or normative reference values. [c] No comparison provided/impairment quantified by reporting proportion of PLHIV with deficits. [d] Controls performed worse.

3.3.3. Static balance

Five studies assessed static balance using clinical tests. One study[264] assessed Romberg eyes-closed-on-foam and found the frequency of impairment to be higher in PLHIV. Tandem stance time was normal in PLHIV.[33] Four studies assessed single leg stance time.[2,3,32,33] Impairments were noted either only with eyes closed, or with synergistic obesity, or when standing on the non-preferred leg (eyes open and closed).

One study[114] assessed COP sway path using a force plate, and found the incidence of increased values to be larger in advanced stages of infection and task difficulty. Sway velocity was examined by another study.[115] A significant increase was found in neurologically symptomatic PLHIV regardless of visual condition, and about 25% of PLHIV with asymptomatic HIV infection also demonstrated increased values.

Average velocity in anterior-posterior (AP) and average velocity in lateral (LAT) directions were assessed by one study.[263] PLHIV with asymptomatic HIV infection had significantly increased AP only in the eyes closed condition, while PLHIV with symptoms of chronic HIV disease had significantly increased AP both with eyes open and eyes closed, as well as significantly increased LAT (only with eyes closed).

Two studies[115,263] assessed the coefficient of the preferential direction of movement (AP/LAT ratio) and found this to be normal in PLHIV. Romberg ratio of area (RA) as well as Way (average velocity of movement) was found to be increased in all HIV groups.[263]

Sensory Organisation Test (SOT) sway strategy score was found to be lower (which is worse, as it indicates more reliance on the hip strategy as opposed to the ankle strategy) for bilateral stance (eyes closed) in PLHIV.[32] Two studies[32,113] reported on SOT Equilibrium Quotient (EQ) and reported significant impairments in PLHIV during the most difficult SOT subtests (eyes closed or inaccurate visual input).

Meta-analyses (Figures 3.2 and 3.3) were performed for postural sway area.[115,263] With eyes open, asymptomatic PLHIV and controls had similar sway areas, while PLHIV with symptoms of chronic HIV disease demonstrated a significant increase. Overall, sway area was significantly increased in PLHIV (combined group of those with and without symptoms of HIV). With eyes closed, PLHIV with asymptomatic HIV infection had normal sway areas, while PLHIV with symptoms of chronic HIV disease demonstrated a significant increase. Overall, sway area was increased in PLHIV.

Thus, the observed overall strength of association for treatment in the combined group differed across the different subgroups. Homogeneity seems to exist between the sample estimates within the subgroups (I^2 = 0.00% for all groups), while a significant interaction existed between the subgroups (I^2 = 86.40% & 87.90% for the two outcomes, respectively), suggesting that the population parameters estimated by the subgroups are different. It should however be noted that the conjecture about homogeneity between sample estimates in these subgroup does not necessarily mean that the presence/absence of symptoms in PLHIV fully explains the heterogeneity observed across studies. In fact, the small number of studies and sample sizes for these outcomes might not provide adequate statistical power in demonstrating heterogeneity.

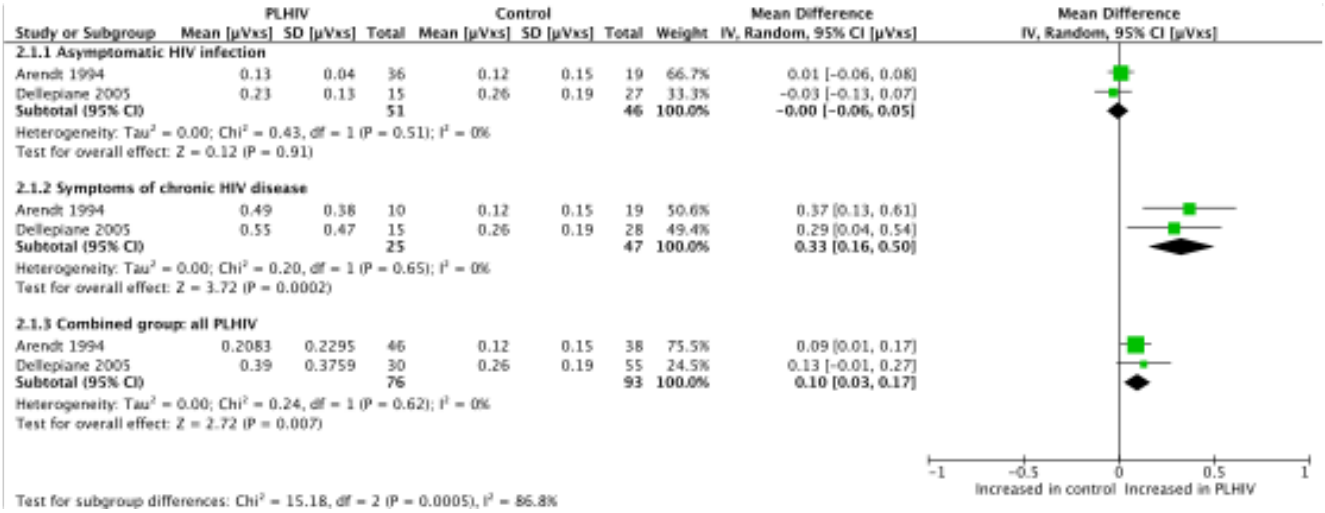


Figure 3.2. Meta-analysis of sway area (μVxs) in PLHIV, eyes open.

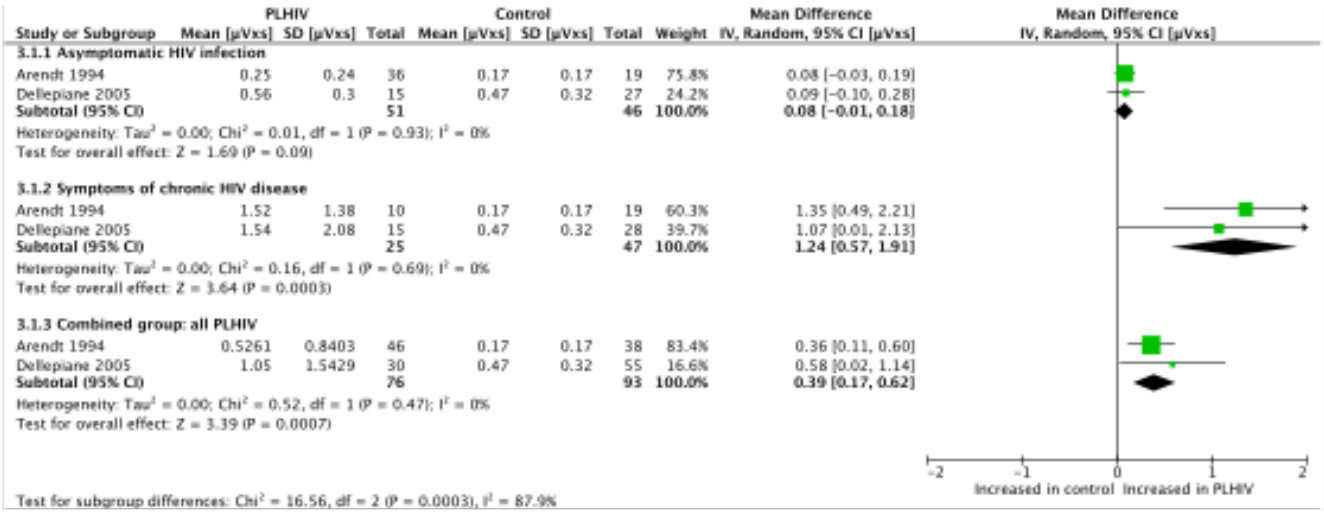


Figure 3.3. Meta-analysis of sway area (μVxs) in PLHIV, eyes closed.

A meta-analysis (Figure 3.4) was done for Romberg ratio of sway velocity (sway with eyes closed/sway with eyes open).[115,263] PLHIV with asymptomatic HIV infection had normal values, while PLHIV with symptoms of chronic HIV disease demonstrated a significantly larger Romberg ratio (which is worse as it indicates a higher amount of visual dependency). Overall, Romberg ratios were similar between the combined group of PLHIV and controls.

Substantial heterogeneity was found within the combined group (I^2 = 88.00%, p = 0.004 and I^2 = 91.00%, p = 0.00001, respectively). When splitting the subgroups according to presence of symptoms, PLHIV with asymptomatic HIV infection still showed evidence of high heterogeneity and non-significant results regarding impairment, while symptomatic PLHIV produced no evidence of heterogeneity (I^2 = 0.00%) whilst showing significant impairment for this outcome.

The high heterogeneity that exists particularly in the asymptomatic subgroup of PLHIV might be attributed to differences in the study populations used by the two studies. Differences existed in the sample sizes used (36 asymptomatic PLHIV in Arendt et al[115] versus only 15 in Dellepiane et al.[263]). Also, the age of the asymptomatic participants in these studies differed (mean of 36.33 versus 28.00 years). Finally, although both studies had similar definitions of "symptomatic" participants, only Arendt et al.[115] further classified the asymptomatic group into CDC disease stages.

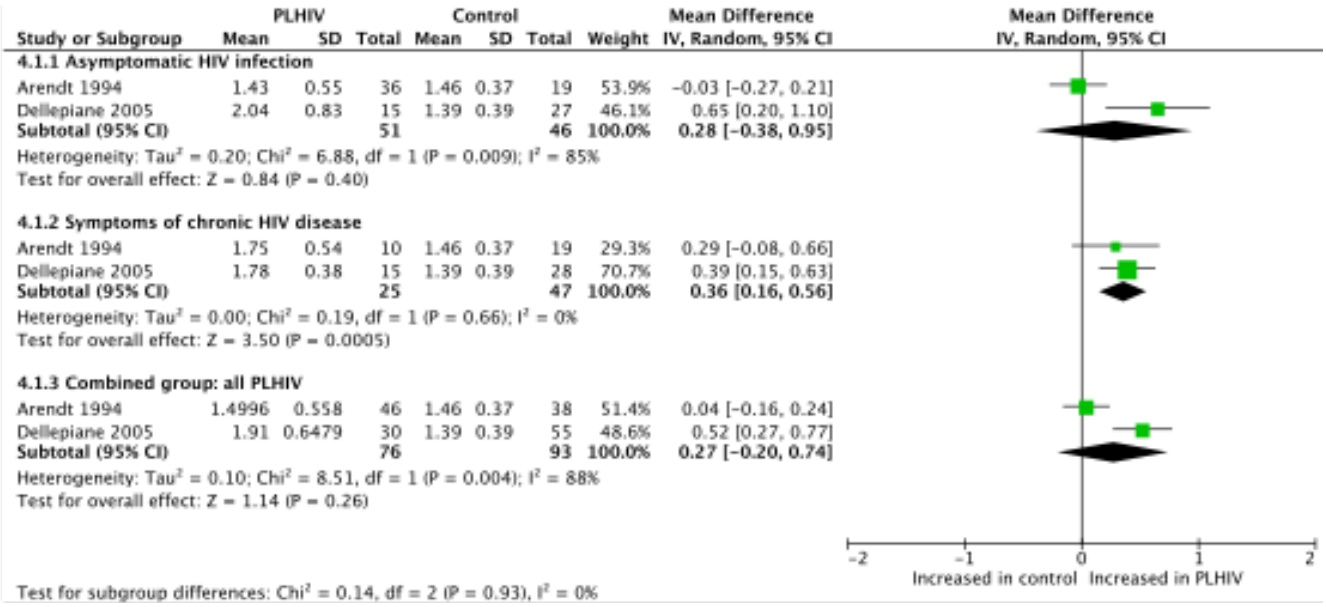


Figure 3.4. Meta-analysis of Romberg ratio of sway velocity in PLHIV.

3.3.4. Dynamic balance

Both the Berg Balance Scale (BBS)[2] and Timed-Up-And-Go (TUG) test[2,3] were normal in PLHIV. For Five-Times Sit-To-Stand (5STS) time, one study[32] found no group differences, while another[2] reported poor performance in PLHIV. The prospective cohort[3] reported an impaired 5STS time at baseline, and that 31% of PLHIV had a decline in performance over one year that was greater than the empirically defined threshold. Only PLHIV who were also obese performed worse in the 360-Degree-Turn test.[32] Walk-Heel-To-Toe was significantly impaired in PLHIV with eyes closed.[33] Two studies[2,49] evaluated forward-reach distance, with no significant deficits noted.

The Functional Base of Support (FBOS) or Limits of Stability (LOS) tests were assessed by two studies[32,113]; both reported significant impairments in all PLHIV.

Duration of postural reflexes was assessed by one study.[263] With eyes closed, there was a significant reduction for medium loop (ML) duration and long loop (LL) duration in all HIV groups. Amplitude of postural reflexes and area of single electromyography (EMG) potential were normal in PLHIV.[263] Neurologically intact PLHIV showed abnormal regulation of postural reflexes (LL amplitude scaling) under unpredictable, but not predictable, perturbations.[262]

Meta-analyses were conducted for postural sway latencies[115,262,263] (Figures 3.5 to 3.9). For the left leg (only specified as the non-dominant leg in one study[33]), short loop (SL) latencies for combined PLHIV groups were normal, with significantly increased values only in PLHIV with symptoms of chronic HIV disease upon further analysis. These findings were similar for the right leg. ML latencies, only assessed in two of the studies[262,263] and only for the left leg, were significantly increased in combined PLHIV groups. In both legs, LL latencies were significantly increased in symptomatic, but not asymptomatic, PLHIV. The combined PLHIV group still showed a significant increase in LL latencies.

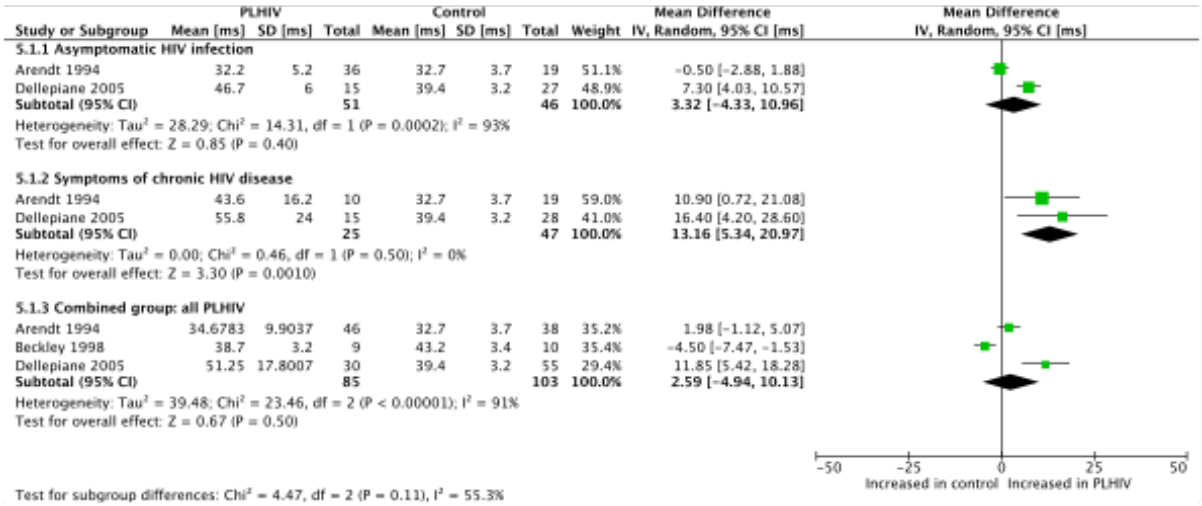


Figure 3.5. Meta-analysis of left leg postural reflex latencies in PLHIV: short loop latencies (ms).

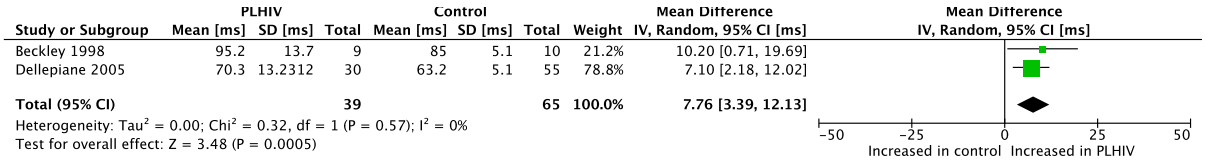


Figure 3.6. Meta-analysis of left leg postural reflex latencies in PLHIV: medium loop latencies (ms).

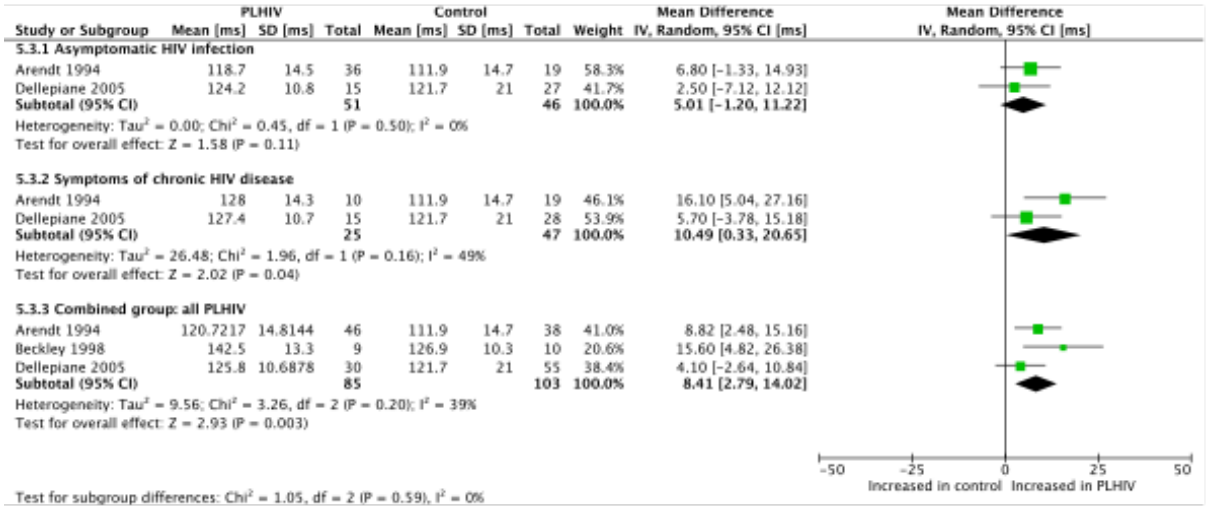


Figure 3.7. Meta-analysis of left leg postural reflex latencies in PLHIV: long loop latencies (ms).

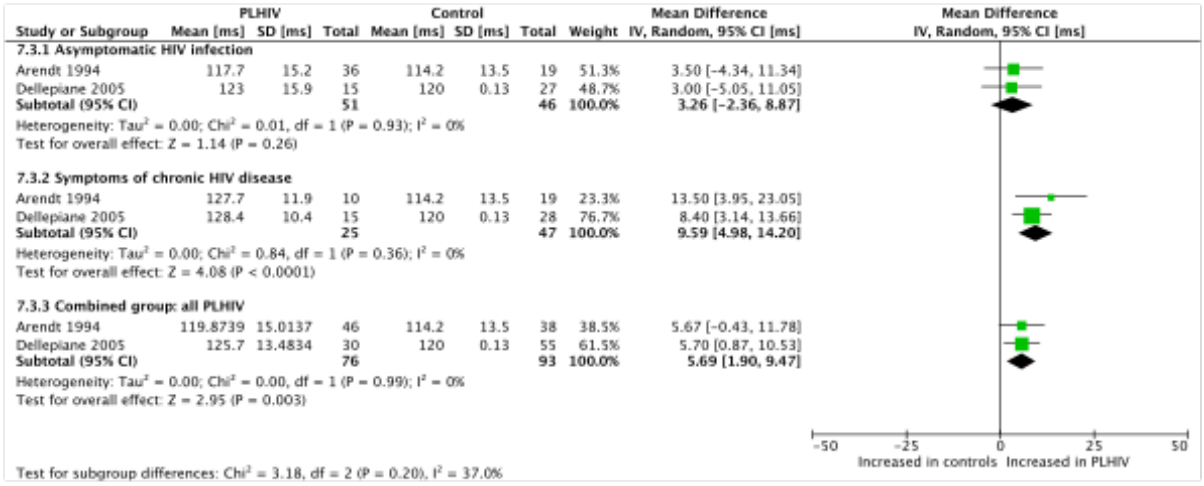


Figure 3.8. Meta-analysis of right leg postural reflex latencies in PLHIV: short loop latencies (ms).

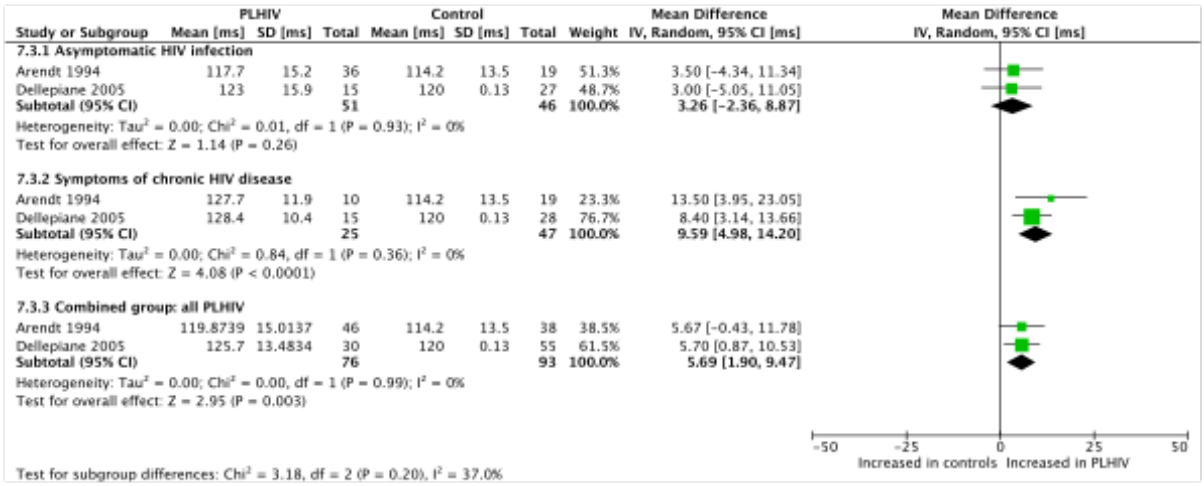


Figure 3.9. Meta-analysis of right leg postural reflex latencies in PLHIV: long loop latencies (ms).

3.3.5. Gait

Gait speed was assessed in eight studies.[3,32,49,55,59,113,260,261] PLHIV demonstrated slowing of fast gait speeds.[49,55,261] One study[113] found no significant differences between PLHIV and controls, regardless of pace.

Meta-analysis[49,51] (Figure 3.10) indicated that Six-Minute Walk Distance (6MWD) was significantly shorter (worse) in PLHIV compared to controls. The likelihood of high

heterogeneity in this meta-analysis should be considered (I^2 = 65.00%, p = 0.09) and might be due to the use of historical controls in one study[49] and differences in disease staging between the two studies. Among the un-pooled studies, three reported a decreased (worse) 6MWD,[2,3,121] and one study found no impairment in PLHIV.[261] One study reported no impairments in PLHIV in cadence[113] and another reported that only PLHIV who were also obese were significantly impaired.[32] This study also reported that PLHIV had significantly delayed (worse) normal gait initiation time.

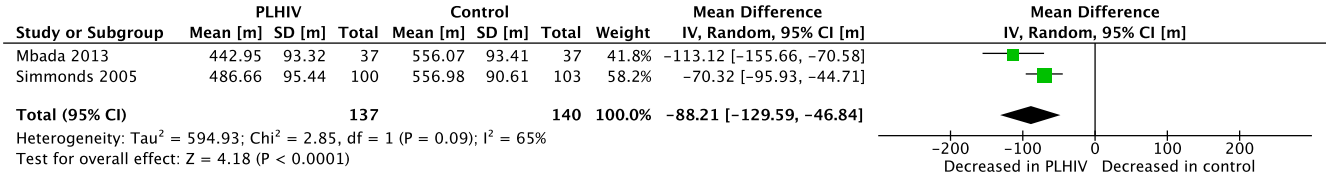


Figure 3.10. Meta-analysis of 6-Minute Walk Distance (m) in PLHIV.

3.3.6. Falls

One study[262] reported that fall incidence during unpredictable perturbations was similar in PLHIV versus controls. Similarly, another study[113] found no group differences in falls during SOT conditions. In contrast, one study reported a similar fall rate in middle-aged PLHIV (mean 52 years) and seronegative older adults (≥65 years).[55] Impaired balance was a major associated factor. In addition, recurrent fallers had significantly slowed gait versus non-fallers. Furthermore, in a prospective cohort,[3] it was reported that 12% of PLHIV experienced a minimum of one fall in the previous year. In PLHIV with recurrent falls, baseline 5STS time and 6MWD were significantly impaired, compared to non-fallers.

3.3.7. Measurement conditions and task difficulty

Twelve studies included some form of increasing task difficulty, such as different visual input, stable versus unstable support surfaces, decreased base of support, predictable and unpredictable external perturbations, and walking at preferred versus fast gait speeds. Of these, nine (75%) demonstrated that both balance and gait impairments were more evident in more difficult task conditions, when comparing PLHIV to controls.[32,33,49,55,59,113,114,262,264]

3.3.8. Disease severity

Fifteen studies reported on the relationship between HIV-disease severity and locomotor performance. Of these, eight (53%) indicated a relationship between HIV-disease severity and impairments.[2,59,113–115,121,262,263] In contrast, seven studies (46%) found no significant differences based on CD4+ counts or viral loads.[3,32,33,49,261,262,264]

3.3.9. Treatment association

Seven studies reported on the relationship between ART and impairments in gait and/or balance, and none of these found any association.[2,3,32,33,59,113,121]

3.3.10. Peripheral neuropathy

Five studies reported on the association between peripheral neuropathy and impairments in gait and/or balance in PLHIV, and none of these found statistically significant correlations between peripheral neuropathy and impairments of gait, dynamic balance or static balance.[2,33,113–115]

3.4. Discussion

The aim of this review was to establish the current state of knowledge regarding objective impairments of gait and balance in PLHIV, and to emphasise those which could contribute to increased fall risk. To the authors' knowledge, this is the first work to do so. The findings indicate that certain aspects of gait and balance are impaired in middle-aged PLHIV, resembling those proven to predict increased fall risk in elderly populations.

The methodological quality of articles ranged from fair to low, partly as a direct consequence of observational design. Earlier studies in particular had a high risk of selection bias due to omitting important information such as participant demographics and exclusion criteria. The psychometric properties of the different tests used to assess outcomes have not yet been evaluated in PLHIV; therefore, they cannot be assumed to be valid and reliable in this specific population. Balance and gait in PLHIV may be influenced by various factors apart from HIV-status. Although studies on average controlled and adjusted for many key confounders such as age, gender, BMI, markers of HIV and co-morbidities, very few reported on covariates such as level of education or adherence to treatment, and none on level of physical activity.

Various gait and balance parameters, including slowed gait speed,[255] cadence,[265] slowed gait initiation time,[266] slowing of postural reflexes,[267] and increased COP displacement and velocity[268] have been established to be associated with increased risk of falls in the elderly. Similarly, some of these variables are associated with risk of falls in PLHIV, namely slowed gait speed and impaired dynamic balance.[55] It has been reported that the best fall risk predictors in PLHIV are those proven to be predictors of fall risk in the elderly.[55]

3.4.1. Static balance

Static balance is often quantified in terms of COP movement,[269] which reflects neuromuscular control to keep the COM within the base of support's limits of stability.[270–272] Increased COP movement and velocity is associated with increased fall risk in the elderly.[268] In this review, evidence of increased postural sway or velocity was found in all studies evaluating these parameters, especially under challenging conditions,[114,115,263] and was confirmed by meta-analyses. Impaired COP sway in PLHIV with asymptomatic HIV infection may suggest early involvement of postural control due to direct infection of the CNS by HIV. However, in neurologically symptomatic PLHIV, it cannot be assumed that anatomical structures or direct HIV-involvement of the CNS causes the observed deficits.[114] Lower limb muscle impairment might impair a person's ability to correct a shift in the body's COP to effectively prevent a fall.[273] In the elderly, it has been proposed that increased COP movement may be interpreted as an increase in hip abductor muscle activity to control postural stability on the medial-lateral direction.[273] It has also been suggested that decreased postural control with larger body sway increases tibialis anterior/soleus muscle co-activation, inducing the hip-strategy to preserve balance.[274] Greater co-activation may be partly be a compensation for decreased lower limb muscle strength and power.[275] As lower limb muscle impairments occur in PLHIV, this might contribute to the impaired COP parameters observed. HIV-associated vestibular dysfunction has also been reported.[276] Vestibular disorders have a deleterious effect on postural stability[277]. However, vestibular conditions are not characterised by impaired COP excursion, but rather by an increased frequency of movement, indicating poor control of COP.[277]

A lower sway strategy score (the relative amount of high-frequency ankle versus low-frequency hip movement) for bilateral stance with eyes closed was found in PLHIV, albeit only reported in a single study in this review,[32] indicating a greater reliance on the hip-strategy. In the general population, individuals without balance impairments will change their balance strategy from the normally employed ankle strategy, to relying on the hip strategy[270] when faced with more challenging conditions. Individuals with impaired balance, who already rely more heavily on the hip strategy, are less able to adapt to challenging conditions.[270]

The SOT Equilibrium Quotient (EQ) is a calculation of the average COP sway, with lower EQ scores having been associated with increased fall risk in the elderly.[278] The two studies evaluating this outcome[32,113] reported significantly lower EQ scores in PLHIV, especially with more challenging conditions.

Reduced single leg stance time is predictive of some (i.e. injurious), but not all, falls in the elderly[279]; however, the clinical value of this test might be called into question. The test might suffer from learning effects,[280] leading to possible ceiling effects even in individuals with substantial impairment when only performed as a clinical test. Due to differences in the reporting of results among the included studies assessing this outcome, it is difficult to draw conclusions regarding impairment and the value of the test in PLHIV.

3.4.2. Dynamic balance

Dynamic balance is often assessed using dynamic posturography, which involves external perturbations being induced while a person tries to maintain an upright posture.[270] A common postural synergy in this scenario is the distal-to-proximal ankle strategy, involving a short loop (SL) and medium loop (ML) response in the gastrocnemius, followed by a long loop (LL) response in the tibialis anterior.[281,282] Prolonged stance-stabilising LL responses have been documented in elderly fallers.[283] Meta-analyses indicated that LL latencies were increased in symptomatic but not asymptomatic PLHIV, and upon combining all groups of PLHIV, LL latencies were still significantly increased. It is suggested that the early-observed prolonged LL latencies in PLHIV with asymptomatic HIV infection may indicate alterations in the central dopaminergic system (basal ganglia, caudatus nucleus and nigrostriatal system).[263]

Scaling of LL latency-amplitude, referring to the ability to adjust the size of postural stabilising reflexes and another important factor associated with falls,[267] was assessed in one study.[262] Neurologically intact PLHIV showed abnormal postural reflex regulation under unpredictable, but not predictable, perturbations. Under random conditions, PLHIV automatically selected a LL response of a relatively similar size to one needed for medium perturbations. This response may not be sufficient to correct for large perturbations, leading to an increased risk of falling. However, the authors noted that the impairment in PLHIV was “mild” and did not appear clinically significant in early HIV infection.

The Limits of Stability (LOS) or Functional Base of Support (FBOS) test involves instrumented measurement of a forward leaning task and evaluates voluntary control of the center of gravity (COG). Instrumented LOS or FBOS, unlike the clinical Functional Reach test,[2,49] was impaired

in PLHIV.[32,113] Similarly, the Functional Reach test has been proven not to be an indicator for differentiating elderly fallers from non-fallers,[284] while instrumented LOS is an early indicator of increased fall risk in the elderly.[285] These observations may be attributable to the differences in the task involved in the clinical versus the instrumented tests (although both assesses LOS).[285]

The 5STS test is an indicator of dynamic balance. Impaired performance was noted in two of the three studies evaluating this outcome.[2,3] In addition to impaired central sensorimotor components being proposed to play a role,[3] impaired 5STS time also implies poor lower limb muscle performance, which is associated with falls and disability both in HIV-seronegative elderly populations and in middle-aged PLHIV.[2,55] Low appendicular muscle mass is prevalent in PLHIV and associated with functional impairment.[120] However, a decline in the ability of muscles to produce strength and power (dynapenia) might have a bigger contribution to functional decline in the elderly and is associated with poor chair-rise-time.[123] Intra-muscular impairments, including fatty muscle infiltration, and low central activation are reported in PLHIV[121,124,125] and premature expression of genes associated with muscle aging is upregulated in PLHIV.[127] Grip strength might correlate with dynapenia in the elderly,[286] and an accelerated decline in grip strength has been reported in PLHIV.[287]

Owing to the dichotomous assessment by clinical tests of the ability to maintain standing balance, such tests only detect impaired balance once compensation strategies fail.[270] Selection of effective compensation strategies to restore balance (especially by persons who are physically active), might hide impairments, potentially hampering the use of such tests in active individuals or at an early stage of disease.[270] Level of physical activity was not assessed by any studies included in this review; ceiling effects in the results provided by the clinical balance tests can therefore not be excluded.

Although more suited to quantification of balance, interpretation of the results of instrumented posturography is complex. Generally, an increase in COP movement is assumed to reflect impaired balance; but this may not be true.[288,289] Due to the interdependent relationship of the underlying systems, selection of an alternative compensation strategy to maintain stance could lead to observation of either increased or decreased COP movement, which in fact would reflect optimal balance control.[270] Second, altered COP movement can result from deterioration of several underlying systems. Thirdly, COP movement is affected by training and learning effects, for example, individuals (and even more so those trained in sports) might be able to maintain a position very well, despite severe system deterioration, due to becoming familiar with the task or using selecting proper strategies for efficient compensation.[270] Results,

especially from singular studies, must thus be considered cautiously and in the context of the assessment protocol, e.g. number of trials, and participant characteristics, such as activity level.

3.4.3. Gait

In this review, PLHIV exhibited impaired fast, but not preferred, gait speeds, despite being on successful HAART.[32,49,59,260] PLHIV who were also recurrent fallers, had an even slower fast-paced gait.[55] Gait speed is reported as a predictor of falls in geriatric populations, with a linear relationship between slow gait speed and increased fall risk often assumed.[250,290,291] However, a non-linear relation has also been proposed.[255] Growing evidence show that gait and cognition, specifically attention and executive function[292] are interrelated. Neurocognitive decline occur in HIV,[6,25,293–295] is in part associated with reduced dopaminergic function,[296] and has been associated with slow gait speeds in this population.[297] Executive function, motor skills and attention/working memory are some of the domains that are affected by HIV.[298] Gait slowing is suggested to be an adaptive mechanism to prevent falls, to the effect that a slow gait speed might actually be associated with a reduced fall risk.[255]

Six-Minute Walk Distance, which is actually an indicator of functional aerobic capacity, has been shown to correlate well with gait speed.[299] Meta-analyses of two studies[49,51] suggests decreased 6MWD, and thus decreased gait speed under fast conditions, in PLHIV. Six-Minute Walk Distance was also reported to be decreased in PLHIV in the majority of un-pooled studies assessing this outcome[2,3,121] – however all of these studies used predicted values from the literature. This is of concern, as community-specific or cultural factors influence gait speed.[261] Gait initiation time was reported to be significantly slowed in PLHIV, albeit data from a single study.[32] Gait initiation time has been associated with increased fall risk in the elderly.[266] Cadence, which also has an association with gait speed and falls in the elderly,[300] was assessed by two studies,[32,113] but owing to contradicting results, no firm conclusions can be drawn.

3.4.4. Measurement conditions and task difficulty

Evaluating performance under conditions of varying difficulty can provide more “real-life” insight into the quality of the specific underlying sensory systems.[270,301] Studies assessing balance included in this review employed different sensory conditions, eliminating or disturbing the information of three main sensory systems. These included variations in visual input, different base-of support sizes and variations in support surfaces. For dynamic balance

assessments, perturbations of varying amplitudes and predictability were induced using platform tilts. There was an overall tendency of PLHIV to perform similar to controls in easier conditions, and significantly worse with increased task difficulty. A correlation between static balance deficit and eyes closed conditions was demonstrated by clinical as well as instrumented tests.[32,113,263] Unstable conditions with eyes closed showed the greatest abnormalities in postural balance.[114,264] Sullivan et al.[33] found impaired performance among PLHIV during clinical tests involving reduced base of support. Postural reflex synergies also appear to be task-dependent. Unpredictable perturbations resulted in worse dynamic balance performance.[262] It thus seems that PLHIV may have impaired response to unexpected perturbations or more complex tasks, predisposing them to falls. In the case of impairment of any of the systems contributing to postural balance, alternative compensation strategies are used by an individual to maintain postural control and orientation.[270,302] Sensory reweighting comes into play, i.e. the nervous system will rely on more accurate sensory input, rather than less accurate, conflicting information[303]. Individuals relying more on one particular balance system are thus less able to adapt to situations where input to that system is disturbed, and have to rely on only the remaining systems.[270] This sensory reweighting seems impaired in PLHIV. Also, impaired dual-task performance has been demonstrated in PLHIV,[186] although none of the included studies assessed this condition.

All gait tests in included studies were conducted on level, unobstructed walkways. During walking, many falls occur not during normal walking, but rather when negotiation challenging terrains. Results might have been more clinically relevant had irregular or unfamiliar surfaces been assessed, especially since dynamic balance in PLHIV seem to be more impaired under challenging circumstances. However, both self-selected and fast gait speed conditions were evaluated, with group differences mostly found when comparing fast gait. It has been suggested that walking at different speeds likely influences both the noise level in human motor performance as well as dynamic error corrections.[236] Thus, impairments at fast paced conditions may indicate deficits under more challenging conditions.

3.4.5. Disease severity

A dose–response relationship between HIV disease severity and locomotor impairment was suggested in 53% of studies. In addition, subgroup analyses highlighted impairments in postural reflex latencies that were inconspicuous in a combined group of all PLHIV, but became apparent in only those with symptoms of chronic HIV disease when compared to controls. However, methodologically it remains a challenge to attribute observed differences between PLHIV and controls directly to HIV infection, as evident from the discussion thus far.

Comparison populations most likely always differ in terms of many confounding factors.[2] It cannot be assumed with certainty that observed impairments are purely related to severity of HIV infection, and the contribution of various comorbidities and opportunistic infections should be considered. This is especially true for the older studies, where eligibility criteria did not control for various confounders and comorbidities.

3.4.6. Treatment associations: antiretroviral therapy (ART), combination antiretroviral therapy (cART) or highly active antiretroviral therapy (HAART)

The majority of studies reporting on treatment associations failed to find significant relationships with balance or gait outcomes in PLHIV, regardless of the different combinations of drugs (terms used for combination use of ARV including ART, cART or HAART). Thus, antiretroviral therapy does not appear to be significantly associated with impairments in locomotor function.

3.4.7. Peripheral neuropathy

None of the five studies reporting on the association between peripheral neuropathy and locomotor impairments found any significant relationships. A possible explanation for balance abnormalities among PLHIV, at least for those parameters measured by the included studies, might thus indicate involvement of the central rather than peripheral nervous system.[2,33,113–115] The fact that eyes closed conditions were often necessary to elicit group differences in balance, further motivates CNS dysfunction as an underlying mechanism.[113] It is reported that deficits in infratentorial brain tissue volume and disruption of the pontocerebellar fibre system microstructure, at least in part, may contribute to locomotor impairments in PLHIV.[33] It can, however, not be concluded with certainty that no association exists between gait or balance and peripheral neuropathy in PLHIV. It is possible that peripheral neuropathy adversely affects gait and balance parameters that were not measured in these studies. For example, impairments in joint kinematics (assessed by none of the included studies in this review) have been associated with peripheral neuropathy in Type 2 diabetic patients.[112]

3.4.8. Implications for future research

While the importance of identifying spatiotemporal deficits is acknowledged, the associated kinematic and kinetic data can provide more insight into underlying mechanisms of the observed impairments. Some locomotor impairments related to early functional decline might

be too small to be detected by visual observation alone in the clinical setting.[265,304] These subtle impairments may however have substantial consequences for the individual. Thus, there is a need for more robust quantitative assessment, such as three-dimensional biomechanical motion analysis. Dual tasking should also be evaluated in PLHIV to assess the subtler changes in function, as well as more challenging gait assessment conditions. Furthermore, a need exists for higher quality research. Carefully selected, representative samples will make results more homogeneous, relevant and generalisable. In addition, valuable information can be extracted from the geriatric literature that is likely to inform research in PLHIV, especially with regards to data on falls and specific movement impairments. This should be further explored, and the psychometric properties of both instrumented and clinical gait and balance assessments should be determined specifically in PLHIV. Lastly, we found the lack of studies conducted in Sub-Saharan Africa, the epicentre of the HIV epidemic, surprising. More research is needed in developing countries to address this gap.

3.4.9. Review limitations

Language bias is likely in this review, as only studies published in English were considered. Another limitation of the review is that only two included articles were appraised by more than one reviewer, meaning that fifteen of the seventeen articles were scored for methodological quality by only one reviewer. In addition, ceiling effects might have hampered results from clinical tests. No studies in this review measured COM movement, with a subsequent incomplete representation of balance in PLHIV at present. Results of this review should be interpreted with caution as substantial statistical heterogeneity existed between the included studies, albeit expected, as evident in the meta-analyses (indicated by high I^2 values). Due to the small number of studies per outcome, all sources of heterogeneity could not be accounted for, but some possible explanations for variation in results have been discussed. Clinical heterogeneity was evident in the majority of studies, particularly in terms of setting, sample sizes, age groups, gender distributions, and HIV-staging. A wide variety of study outcomes and measurement methods were used. Given the paucity of research on existing impairments and the optimal method of evaluating these in PLHIV, the wide variation in assessment tests used was to be expected. Although the diversity in populations, especially regarding disease definition and subgroups, might seem surprising, it must be kept in mind that HIV classification systems have evolved substantially since the earliest included study and that HAART regimes did not yet exist in those earlier periods. Furthermore, publication- and reporting biases are suspected in this review, due to many authors collaborating on different papers and the same

populations possibly used in different studies. However, formal assessment using funnel plots was not possible due to the low number (<10) studies assessing a similar outcome.

3.4.10. Chapter summary

This review found that young to middle-aged PLHIV have impairments in certain aspects of gait and balance, which are similar to those that predispose elderly seronegative populations to falls. The impairments are more pronounced during challenging conditions, might be associated with HIV disease severity, are not influenced by ART, and might not necessarily be associated with peripheral neuropathy. Results should be interpreted with caution due to the overall fair to low methodological quality, substantial heterogeneity and many outcomes being assessed by singular studies only. The effect of HIV on gait and balance parameters, and in particular biomechanical outcomes, are currently insufficiently quantified and this review provides a first step to inform future research. Further investigation involving more methodological uniformity is warranted to better identify and understand relevant locomotor impairments in PLHIV. Only then can more clinically relevant conclusions, such as appropriate strategies for fall-prevention in this population, be drawn.

The next part (Part II) of the dissertation sought to ascertain the validity and reliability of a newly-acquired portable three-dimensional gait analysis system for measuring custom-defined gait analysis outcomes. Gait assessment was the major focus of this dissertation, given the large gap in knowledge and the fact that gait outcomes were also to be used in calculating summary score to validate selected clinical tests (Chapter 7).

Based partly on the results from this review, four traditional centre of pressure (COP) metrics were also chosen for evaluation of postural stability (excursion and velocity, in two movement directions). Given that these were not complex measures, and since the motion laboratory was already in possession of a validated pressure mat that has been widely used in clinical practice and research, the psychometric properties of the mat were not assessed in these participants, as there was no reason to doubt its validity and reliability.

3.5. Declaration by the candidate

With regard to Chapter 3 (pp. 42-78), the nature and scope of my contribution were as follows:

Nature of contribution	**Extent of contribution (%)**
Conceptualisation and writing of manuscript, literature search, data extraction and analysis, critical appraisal of all studies, data interpretation and final editing.	75%

The following co-authors have contributed to Chapter 3 (pp. 42-78):

Name	**e-mail address**	**Nature of contribution**	**Extent of contribution (%)**
Prof. Quinette Louw	qalouw@sun.ac.za	Supervisory role: Research inputs, editorial suggestions and proofreading.	10%
Dr Linzette Morris	ldmorris@sun.az.za	Critical appraisal of two articles, literature recommendations, data interpretation and proofreading.	10%
Prof. Jochen Baumeister	jochen.baumeister@uni-paderborn.de	Literature recommendations, data interpretation and proofreading.	5%

Signature of candidate: **K. Berner**

Date: **April 2019**

3.6. Declaration by co-authors

The undersigned hereby confirm that:

1. the declaration above (p. 79) accurately reflects the nature and extent of the contributions of the candidate and the co-authors to Chapter 3 (pp. 65-102),

2. no other authors contributed to Chapter 3 (pp. 42-78) besides those specified above (p. 79), and

3. potential conflicts of interest have been revealed to all interested parties and that the necessary arrangements have been made to use the material in Chapter 3 (pp.42-78) of this dissertation.

Signature	**Institutional affiliation**	**Date**
Professor Quinette Louw	Division of Physiotherapy, Department of Health and Rehabilitation Sciences, Faculty of Medicine and Health Sciences, Stellenbosch University	April 2019
Doctor Linzette Morris	Division of Physiotherapy, Department of Health and Rehabilitation Sciences, Faculty of Medicine and Health Sciences, Stellenbosch University	April 2019
Professor Jochen Baumeister	Exercise Science and Neuroscience Unit, Department Exercise and Health, Faculty of Science, Paderborn University, Germany	April 2019

PART II
Establishing validity and reliability for clinically relevant gait analysis outcomes in a South African population including people living with HIV-1 infection

Preface

In this dissertation, gait biomechanics were quantified in people living with HIV-1 infection (PLHIV) relative to seronegative participants (SNP) using a newly acquired commercial inertial motion capture (IMC) system. Due to its portability and ease-of-use, such a system overcomes many of the accessibility constraints associated with laboratory-based gait analysis. This system offered a pragmatic solution for translating state-of-the-art gait analysis research into a rural clinical setting.

This methodology required an evidence-based approach to data collection, variable definition and extraction and data interpretation. Three-dimensional optical stereophotogrammetry (from here on forth referred to simply as “optical motion capture” [OMC]) is currently considered the gold standard in instrumented gait analysis[305] and was thus employed as a reference standard in the process of establishing a set of valid, reliable, clinically relevant 3DGA outcomes that could be measured in-field with the IMC system.

Part II of the dissertation subsequently presents two primary interlinked validity and reliability studies, spread over three chapters (Chapters 4 to 6, see Figure below). The first set of testing was performed in healthy volunteers recruited from the university setting to explore the system’s validity and reliability for measuring basic gait analysis outcomes. Following this, the second set of testing involved participants recruited from a rural community (including PLHIV) and a more clinically-orientated gait analysis. This was done to ascertain validity and reliability (including measurement error) specific to the population and outcomes used in the main study of this project (Chapters 7 to 8). As much of the methodology between the first and second studies overlap, Chapter 4 presents the combined methodology – indicating relevance to the specific study where necessary. Chapters 5 and 6 respectively present the results of the first and second validity and reliability studies.

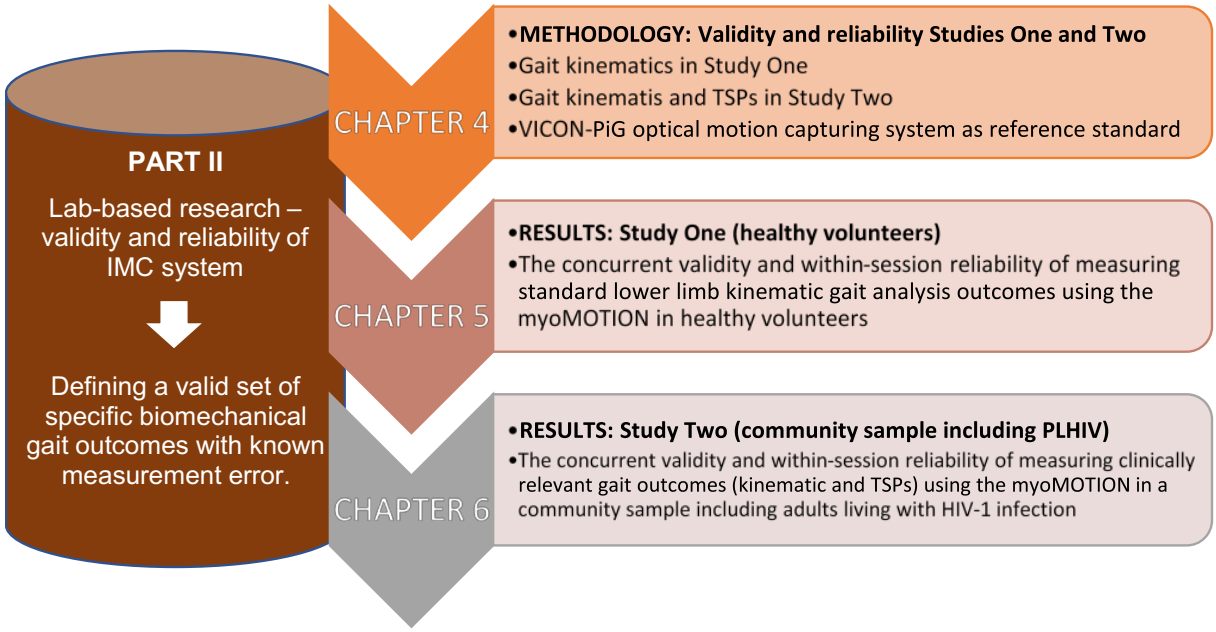


Figure Part II Preface. Schematic layout of the structure of Part II of the dissertation. IMC = inertial motion capture; PLHIV = people living with HIV-1 infection; TSPs = temporal and spatial parameters.

Introduction to the validity and reliability studies

Over recent years, developments in nano- and microprocessor technologies, computing and digital signal processing have led to extensive technological advances in Micro-Electromechanical Systems (MEMS) and resulted in the development of miniaturised portable inertial motion capture (IMC) systems.[189] These systems are based on small yet powerful integrated circuits called Inertial Measurement Units (IMUs), which typically comprise of on-board tri-axial gyroscopes, magnetometers and accelerometers.[189]

IMC systems are increasingly used for 3DGA in research and clinical settings.[189] Despite providing high quality data and remaining the golden standard in motion capture technology, the appeal of OMC in clinical care is hampered by several issues such as high costs, requirement for expert operation, lengthy and cumbersome setup and post-processing procedures, the problem of marker occlusion and limited ecological validity due to capture volumes being restricted to laboratory settings.[204] Since such systems present a barrier to access to clinicians as well as patients, a growing need has arisen for a more pragmatic alternative that is better suited to in-field use. Relative to OMC, IMC systems are compact,

portable, affordable and user-friendly; increasing clinical appeal. Using sensor fusion techniques, the ability of inertial measurement units (IMUs) to accurately track orientation has become advanced, with tracking accuracies of ±1° being reported.[306,307]

The increasing appeal of IMC-use has behoved researchers to further assess the validity and reliability of such systems, and good performance has been demonstrated for specific protocols in healthy participants and patient groups.[308–312] The underlying assumptions and body models associated with testing accuracy and reliability in healthy participants only may not necessarily hold true in pathologic conditions or participants from different communities, as gait characteristics can be varied by anthropometric, racial and cultural factors.[209] Similarly, validity and reliability proven in people living with a specific condition may not be the same for other pathologies. Recent recommendations for standardising validity testing protocols for body-worn motion capture devices emphasise the importance of demonstrating validity and reliability in the specific population of intended use.[313] Measurement error should thus be determined for both healthy participants and patients, to improve the quality of data collection and interpretation; failing to do so may result in misdiagnosis and misinterpretation of clinical impairments and biomechanical gait data.[313]

Data acquired from IMC are known to suffer from various error sources which may reduce their accuracy of analysis. Although theoretically, the motion data measured by IMUs (once processed using relevant algorithms) can estimate important information including orientation, rotation, acceleration and distance, challenges remain in utilising IMUs for quantifying human motion patterns in practical scenarios. Schwartz et al.[313] proposed classifying the potential sources of error as being of intrinsic (occurring naturally via intra-session or inter-participant variability) or extrinsic (due to experimental errors and subject to quality control) origin. Intrinsic errors cannot be reduced but should at least be quantified as a comparison baseline, whereas extrinsic variation may be improved by addressing the underlying methodological sources. Besides natural intra- and inter-individual gait variability (intrinsic variability), it is important to consider the various potential extrinsic error sources during participant preparation, data collection (e.g. anatomical frame calibration errors, soft tissue artefact [STA]), data processing (such as definition of foot contact events) and data interpretation (for example, according to the system-specific biomechanical model).[308,314] IMUs suffer from time-increasing drift in the presence of magnetic disturbances (e.g. induced by ferromagnetic material), necessitating controlled test protocols and efforts to avoid such disturbances whenever possible (as this drift may affect the accuracy of orientation measures by the magnetometer).[189] IMC systems track the angular position of coordinate systems on the body relative to north and gravity (roll, pitch

and course). Joint/segment kinematics can thus be calculated using body segment-mounted IMUs, but due to an inability to measure absolute skeletal position kinematics (i.e. linear position in space), initial calibration is required to determine the heading of the body relative to magnetic north and to compensate angular offset between IMU- and segment axes. Only after model calibration can estimates of translation be made via mathematical techniques.[315]

Various IMC calibration approaches exist, ranging from static single- or double-poses, to dynamic functional calibrations.[189] Single-poses, involving determination of IMU orientations relative to a reference posture,[189] are often utilised by commercial IMC systems such as the myoMOTION (the system used in this research), as they are quick and easy to implement. Importantly, differences in joint segment definitions mean that OMC biomechanical models typically demonstrate angular offsets from the assumed IMC reference neutral pose (N-pose). Although IMC ROM and movement patterns do not seem to be significantly affected, absolute values are often not directly comparable between systems/models.[189,308,316] N-pose accuracy and repeatability may be compromised by skeletal alignment constraints and instructor skills in setting up the posture, and errors introduced during calibration may affect subsequent kinematic measurements. Clearly, such errors need quantification in order to make clinical sense of IMC output.

The reliability and concurrent validity of IMC systems likely depend on the combination of IMUs and biomechanical model. Confirming the validity and reliability of IMC to investigate human locomotion is imperative to future applications outside of the laboratory. At present, no 3D motion analysis system is available that can non-invasively and exactly reflect the orientation of the underlying bone.[317] Results from available systems should thus adequacy exceed the measuring error to provide clinically meaningful results. For instrumented motion capture, absolute errors of less than of 5° has been proposed as reasonable.[318]

The current research used different instrumented outcome measures to assess gait and balance in PLHIV, including a pressure mat (for balance), and the newly-acquired myoMOTION system (for gait). At the stage of its acquisition, the myoMOTION was the first of its kind in South Africa and offered potential enhanced performance,[319] portability and a user-friendly interface relative to other IMC systems available at the time. The system presented a promising opportunity to extend 3D gait analysis to outside the laboratory and without the presence of a laboratory engineer. Although the MatScan pressure mat has previously been validated for measuring COP data during a single-leg stance task,[320] and used for balance assessments in South African populations[321] as well as proven useful for assessing COP data from single leg stance tasks in PLHIV,[322–324] the myoMOTION system

has not been previously validated in a South African population or for the gait outcomes of interest in the current research. Considering that the speed and pattern of gait is dependent on anthropometrics, community and culture,[325] it is important that 3DGA systems are validated in the same or similar populations as the intended future study population.[313]

The purpose of the following two studies were therefore to determine the concurrent validity of the myoMOTION IMC system, using the VICON OMC system as the reference standard, and the within-session reliability of the myoMOTION – first in a set of healthy volunteers, and subsequently in a population including PLHIV and recruited from a rural area in the Cape Winelands of South Africa. Absolute reliability of the outcomes in the population of interest would indicate the change required (in degrees or in the relevant measurement units) to exceed measurement error for gait outcomes used in the evaluation of gait deviations in PLHIV.

PART II

CHAPTER 4
METHODOLOGY: VALIDITY AND RELIABILITY STUDIES ONE AND TWO

Two validation and reliability studies were conducted in a sequential fashion, so as to have findings from Study One refine the hypotheses and practical aspects of Study Two.

4.1. Aims and objectives: Study One

4.1.1. Aim

The first study aimed to determine the concurrent validity and within-session reliability of clinical gait analysis outcomes measured by the myoMOTION system, using optical motion capture (OMC) and the VICON-Plug-in-Gait (PiG) biomechanical model as reference standard.

4.1.2. Objectives

1. To establish concurrent validity for the myoMOTION system by determining whether differences in average kinematic joint/segment angles across the gait cycle would fall below a 5° minimum clinically important difference (MCID) when comparing kinematic angles using (i) direct myoMOTION output and (ii) after removing offsets between the myoMOTION and VICON-PiG models, in a sample of healthy, able-bodied volunteers. It was hypothesised that differences would exceed the MCID for direct comparisons, and fall below it for model-corrected comparisons.
2. To determine whether within-session reliability of the myoMOTION-model-based average joint/segment kinematic angles across the gait cycle would fall below a 5° MCID, using six repeated gait trials.
3. A secondary outcome was to use VICON-PiG to quantify the accuracy and repeatability of a calibration N-pose as set up by a trained instructor, as a source of extrinsic error potentially affecting gait outcomes.

4.2. Aims and objectives: Study Two

4.2.1. Aim

Study Two expanded the findings of Study One in a sample recruited from a rural community (the same that would be accessed for the main study in Chapter 7), including PLHIV and seronegative participants (SNP). The aim was to explore whether similar levels of concurrent validity and within-session reliability to that achieved in healthy volunteers, can also be achieved when assessing clinically relevant gait outcomes in a community-specific cohort including PLHIV and SNP from the Cape Winelands District, Western Cape, South Africa.

4.2.2. Objectives

1. To establish concurrent validity for the myoMOTION system by determining whether differences in joint/segment kinematic ROM and discrete angles would fall below a 5° MCID when comparing angles using (i) direct myoMOTION output and (ii) after adjusting for offsets between the VICON-PiG and myoMOTION models in a sample of PLHIV and SNP. It was hypothesised that differences in discrete angles would exceed the MCID for direct comparisons, and fall below it for model-adjusted comparisons, while angular ROM differences would remain unchanged and below the MCID regardless of model adjustment.
2. To establish concurrent validity for the myoMOTION system by determining whether differences in temporal, spatial, temporophasic and temporospatial gait parameters (TSPs) would fall below the relevant MCID for each when comparing TSPs using direct myoMOTION output to VICON-PiG outcomes in a sample of PLHIV and SNP. It was hypothesised that differences in TSPs would be minimal and display excellent percentage errors (<5%).
3. To determine whether intra-session reliability of joint/segment kinematic ROM and discrete angles measured by the myoMOTION would fall below a 5° MCID, using six repeated gait trials.
4. To determine whether intra-session reliability of TSPs estimated by the myoMOTION would fall below a 5% percentage difference, using six repeated gait trials.

4.3. Ethical considerations

Study approval was granted by the Stellenbosch University (SU) Human Research Ethics Committee (HREC, N15/05/043) (Appendix A) (Studies One and Two) and the Western Cape Department of Health (WC_2016RP10_878) (Appendix B) (Study Two). Written informed consent was obtained from all participants in their preferred language prior to data collection (separate forms for the two studies) (Appendices D and E).

4.4. Study design

Both studies followed an observational design, incorporating an agreement and offset component for concurrent validity testing and a within-session repeated measures observational component for reliability testing. A single testing session was conducted per participant. Study Two forms part of the sub-study (i.e. this PhD project) to a larger longitudinal cohort being conducted by the SU Department of Physiological Sciences/Division of Medical Physiology (Section 4.7.2 provides further details of the overhead study; here on forwards referred to as only the "EndoAfrica" study).

4.5. Study setting

Data collection for both studies was performed in the SU Central Analytical Facilities (CAF) 3D Human Biomechanics Unit, Tygerberg Medical Campus, Cape Town, South Africa, where the VICON system is hosted. For Study One, participants were responsible for their own transport to and from the test facility. For Study Two, participants were transported between Worcester and Tygerberg campus using official SU transport services.

4.6. Sample size

Sample size was based on the standard error of measurement (SEM) for lower limb kinematic angles across the gait cycle, considering an SEM of 4.1°.[326] This was the maximum SEM (hip rotation) reported across tri-planar lower limb angular ROM in a healthy population during habitual walking. An MCID of 5° is suggested for lower limb gait kinematics.[327] To establish that a measured SEM of 4.1° is lower than 5° at a one-sided 95% confidence interval, the recommendations by Stratford and Goldsmith[328] were followed. The variance ratio $\left(\frac{\sigma^2}{s^2}\right)$ was

calculated as $\left(\frac{5.0^2}{4.1^2}\right) = 1.5$. Using Table 7 in Stratford and Goldsmith[328] the required sample size was estimated for a protocol using four to six measurements per participant: a sample size of nine to 15. For Study One, 16 participants were recruited to increase precision and to allow for any data loss due to technical failure or invalid trials. For Study Two, sample size was restricted by pragmatic constraints including the limited and targeted participant pool and the fact that participants had to be transported approximately 94 km between the laboratory and the town of Worcester. Thus, a limited sample comprising both PLHIV and SNP could be accommodated and a convenience sample of 16 adults (eight PLHIV and eight SNP) was deemed practical.

4.7. Study population and sample

4.7.1. Study One

The sample population comprised of able-bodied, HIV-seronegative adults (students and staff) from the SU Tygerberg Medical Campus, Cape Town, South Africa. This population was considered appropriate to facilitate an initial and technical investigation of measurement error between systems in an easily accessible population with normal motor function and minimal gait variability, as well as the assessment of variability on repeat measures of the same individuals,

4.7.2. Study Two

Study Two investigated how the instruments compare in the same population being accessed for the cross-sectional field study, which meant accessing the same population as the overhead EndoAfrica study. The EndoAfrica study is a prospective, longitudinal cohort of PLHIV and SNP followed in community health care centres (CHC) and/or HIV clinics of the Cape Winelands District, Western Cape Province, South Africa. The cohort aims to determine whether HIV-1 infection and antiretroviral therapy (ART) are associated with alterations in cardiovascular risk and in vascular endothelial structure and function. The EndoAfrica study was initiated in April 2015 and includes male and female adults aged ≥ 18 years; excluding females who are pregnant, or less than three months post-partum. Details of the EndoAfrica protocol have been described in detail elsewhere.[329]

4.8. Eligibility criteria

4.8.1. Both studies

Participants were eligible for the study if they were:

1. Adults (aged 18 to 65 years). The upper age limit was based on the observation that, in the general population, gait changes associated with ageing become more prevalent in adults older than 65.[330]
2. Had a BMI < 25kg/m^2. This criterion was introduced to limit the effects of soft tissue artefact (STA) on gait measures. Subcutaneous tissue movement influences the data captured by markers or sensors applied to the skin and this is less likely with lower BMI ranges.[331] In addition, evidence suggests that a higher BMI is a confounder to gait and balance impairments in PLHIV, whereas this is not the case for lower (including underweight) BMI ranges.[32]
3. Were independently ambulant (without any walking aids).
4. Were able to consent and participate in all study procedures.

Participants were excluded if they:

1. Were pregnant (if female).
2. Had an acute illness.
3. Suffered from any neuromusculoskeletal impairments or injury that might affect gait.
4. Had a history of seizures, mental retardation, head injury, stroke, epilepsy, cerebral palsy or other major neurological conditions.
5. Had used alcohol on the day of testing. Acute alcohol consumption has a known detrimental effect on locomotor performance.[332]

4.8.2. Specific to Study One

For study One, in addition to the criteria listed above, participants had to have their HIV serostatus confirmed as HIV-seronegative via a blood test (see Section 4.9.1.1. below).

4.8.3. Specific to Study Two

For Study Two, in addition to the criteria listed above, participants had to fulfill the following criteria:

1. For the HIV-1 seropositive group, participants had to be included in the EndoAfrica cohort with a confirmed diagnosis of HIV-1 infection (via blood test). In accordance with the field study criteria (Section 7.6.2), PLHIV were included regardless of HAART use. The systematic review presented in Chapter 3[62] found that gait and balance impairments are not likely associated with HAART use.
2. For the HIV-seronegative group, participants had to be HIV-seronegative adults from the same community as the HIV-1 seropositive group (either EndoAfrica participants or not). Gait pattern and speed is dependent on community, anthropometrics and culture[325]; therefore, in order to make valid extrapolations, study groups need to originate from the same population as the population of intended future use (hence the decision to extend the testing in healthy volunteers from the university, to healthy participants recruited from the Worcester community). It was considered unlikely that differences would exist between EndoAfrica participants and non-participants, as the same research nurse recruited all participants in the same manner used for the EndoAfrica study. Once screened for the present study by the research nurse, and after agreeing to blood tests, those individuals who did not already have their status confirmed as part of the EndoAfrica study, were counselled by the research nurse and a rapid HIV test (SD Bioline HIV 1/2 3.0 immunochromatographic test kit; Standard Diagnostics, Republic of Korea) was performed at the CHC to confirm their status as seronegative.

4.9. Sample recruitment

4.9.1. Study One

Convenience sampling was used to recruit sixteen HIV-seronegative participants from the SU Tygerberg Medical Campus. A letter of invitation was e-mailed to each university department, as well as to student class representatives, an advertisement was placed in the Faculty newsletter, and flyers were posted on university notice boards. The first 16 consecutive individuals who showed an interest to participate were sent a follow-up e-mail with detailed study information (informed consent form) as well as a checklist with eligibility criteria. One potential participant had to be excluded due to a BMI > 25 kg/m^2, and thus the next volunteer on the list was contacted. If an individual was deemed potentially eligible, a convenient date and time for a brief interview for screening and explanation of the study procedures was agreed upon. Potential participants were made aware of the need for HIV testing, and after signing the informed consent form in person, was referred to Campus Medical Services to

undergo the blood test (see Section 4.9.1.1). All those referred for testing had a result negative for HIV-1-infection. Subsequently, for each participant, a date and time for testing was agreed upon. A reminder text message and e-mail were sent to each participant the day before the scheduled data capturing session. All participants received compensation for time or discomfort caused in the form of a supermarket gift voucher.

4.9.1.1. HIV testing

Linked confidential HIV testing was implemented to confirm participants' HIV-status as HIV-seronegative. Specific written informed consent for HIV-testing was obtained from each potential participant as part of the study consent form. Participants were specifically alerted to this clause in the informed consent form and any questions or concerns were addressed. HIV screening was performed only after the potential participant signed the informed consent form. Testing was done at the Tygerberg Campus Health Services (CHS), situated in the student centre on Tygerberg Campus, by a qualified medical nurse. Appropriate pre- and post-HIV-test counselling was offered to participants. A rapid HIV blood test (blood sample via finger prick) was performed. Should a potential participant, who was unaware of his or her status, have tested HIV-seropositive, they would have been excluded from this study (as stipulated in the informed consent form) and referred to Tygerberg CHS for ongoing psychosocial support and medical care. This was however not necessary for any of the potential participants.

Linked testing involves linking the HIV test results with the individual tested and allows them to receive his or her results.[333] A unique study code was assigned to every participant, which was linked to personal identifying information. Thus, while the HIV result was linked to the participant's name via the unique study code, the participant remained anonymous to all but the testing nurse and the researcher (PhD candidate). After the linked confidential HIV testing was performed, the test result was given to the participant. This procedure of confidential (as opposed to anonymous) HIV-testing was a necessary step, as any potential participant who may have tested HIV seropositive would have had to be excluded from the study by the investigator.

4.9.2. Study Two

A convenience sample of 16 adults (eight PLHIV and eight SNP) was recruited from Worcester. Participants were enrolled from a local CHC in Worcester, making use of a shared (with EndoAfrica study) Health Professions Council of South Africa (HPCSA)-registered

research nurse. Participation in the laboratory-based study was proposed to potential participants by the research nurse, who also performed eligibility screening. For the HIV-1 seropositive group, participation was proposed consecutively to individuals already participating in the EndoAfrica study (until eight suitable participants were identified). For the HIV-seronegative groups, current participants in the EndoAfrica study were similarly approached; however, due to a lack of available HIV-seronegative EndoAfrica participants at the time, individuals from the local community and attending the CHC were also invited to participate by the research nurse. The same strategy was used as for recruiting control participants for the EndoAfrica study. Study information was provided, including the need for HIV-testing as part of the eligibility criteria. Following the explanation of study information and once the participant signed the informed consent form, participants with unconfirmed serostatuses were counselled for HIV testing and screened for HIV infection using a rapid HIV test (SD Bioline HIV 1/2 3.0 immunochromatographic test kit; Standard Diagnostic, Republic of Korea). Should this test have been found positive, the individual would have been excluded from the study, counselled and managed further at the HIV clinic – however, this was not necessary for any of the screened participants. Following confirmation of a negative HIV-serostatus, enrolled participants' availability during the testing period was confirmed; this was also done at the time of enrolment for the HIV-seropositive EndoAfrica participants. The most convenient dates and times for transport to Tygerberg Medical Campus and testing was agreed upon and participants received a card with the date and time to report to Worcester CDC for transport to Tygerberg Medical Campus. The PhD candidate, assisted by the research nurse in Worcester, arranged for participants to be transported by a University vehicle to the SU Tygerberg Medical Campus. For those with mobile phones, a reminder text message was sent the day before the scheduled data capturing were to take place. Participants were transported to the motion laboratory using official SU transport services (in groups of two to four, depending on participants' availability) and received a light lunch as well as compensation for time and inconvenience in the form of a grocery store gift voucher.[334] Figure 4.1 illustrates the eligibility criteria and recruitment of participant groups in Study Two

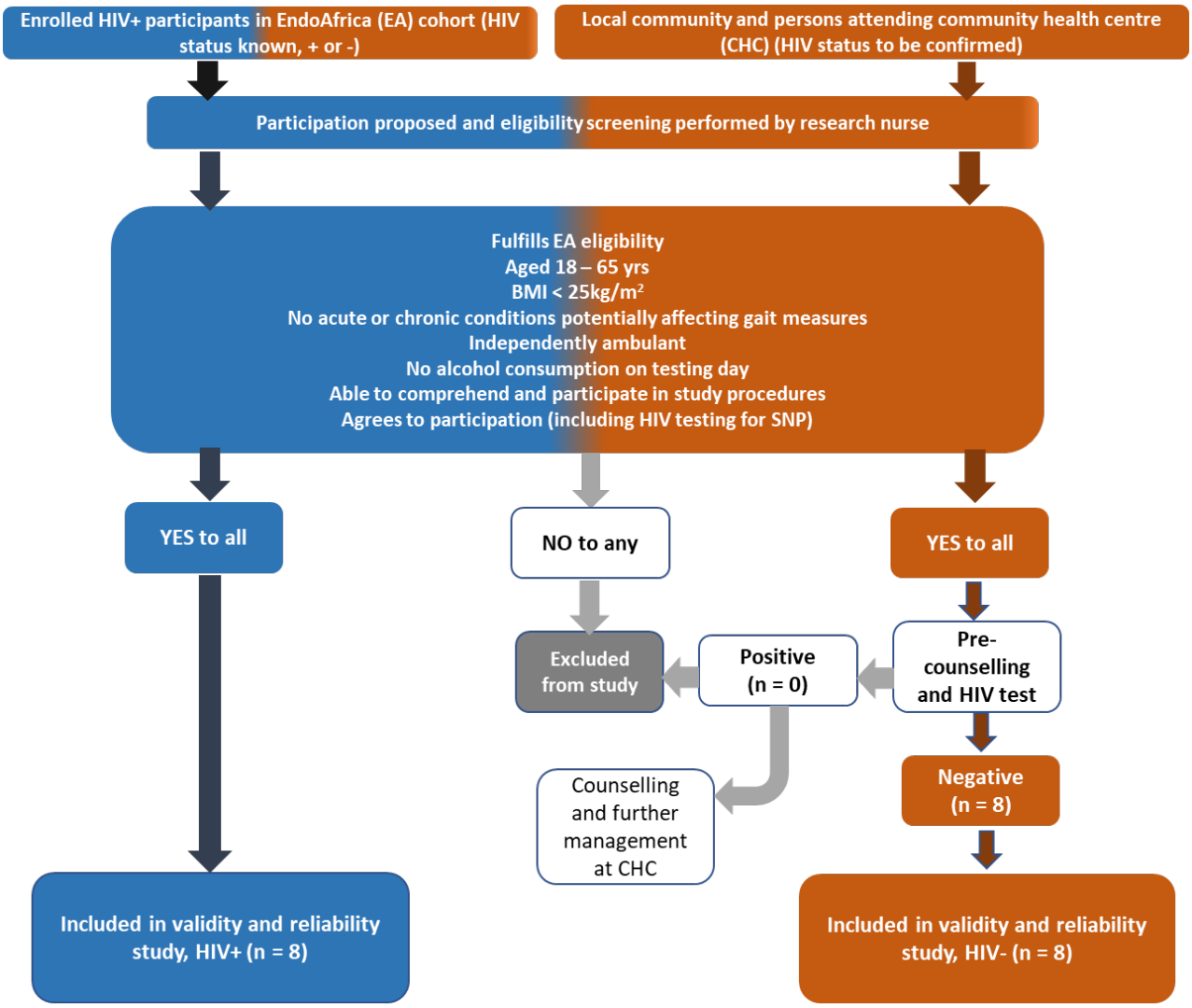


Figure 4.1. Sample recruitment and eligibility criteria for Study Two.

4.10.Instrumentation

Data were collected concurrently at 200 Hz using an eight-camera OMC system (MX T-series, VICON Motion Systems Limited) and a seven-IMU IMC system (myoMOTION Research Pro, Noraxon USA Inc.). Gait events were detected for VICON outcomes using a time-synchronised, floor-embedded force plate (Model FP9060-15, Bertec Corporation) and for myoMOTION using an IMU-based algorithm provided by the system software (myoRESEARCH 3.10.64). The reference and index systems are presented in more detail in the following two sections.

4.10.1. VICON optoelectronic motion capture system (reference standard)

The VICON OMC system (MX T-series, VICON Motion Systems Limited, Oxford, UK) was used to concurrently collect the same data as the myoMOTION index system, thus serving as reference standard in both studies. OMC systems, along with the Conventional Gait Model (CGM; commercially implemented as the Plug-in-Gait [PiG] model by VICON) are often used as a ‘‘gold standard’’ in human motion analysis. This is due to the accurate positional information provided by OMC systems and the fact that the CGM constitutes the most widely used and validated biomechanical model in clinical research.[335] The VICON has previously demonstrated high validity and reliability,[336] with a measurement error of less than 1.5°.[337,338]

The high-resolution, high-speed VICON cameras are specifically designed for motion tracking. The VICON T-series uniquely combines high-speed accuracy and resolution; possessing a resolution of 1-mega pixels, capturing 10-bit grey scale images using 1120 × 896 pixels, and having the ability to capture speeds of up to 250 frames per second. The system uses the multiple synchronised cameras to reconstruct body posture and provides body segment position (origin) and orientation (axis directions) relative to a global fixed coordinate system (GCS).[189]

VICON motion tracking is marker-based, utilising passive skin markers (coated with a retroreflective material) to reflect infra-red light that is generated near the observing cameras’ lenses, back to the various cameras. The markers are placed on pre-specified anatomical landmarks of the body segments to be tracked. The three-dimensional position of a marker can be calculated once it is visible to two cameras at the same point in time. By estimating the coordinates of individual markers and using triangulation, the 3D position of a participant can be modelled within a virtual motion capture volume between at least two cameras calibrated to provide overlapping projections.[339] The cameras are calibrated relative to a ground-fixed reference frame to obtain their position; this is done using an inanimate calibration object with markers attached at pre-defined positions. For motion analysis, at least three markers must be attached to the same rigid body segment to enable tracking of the angulation of that segment’s technical frame within the reference frame.[339] VICON Nexus software (Nexus 1.8.5) automatically determines the centre of each marker and reconstructs their position in the GCS; a process typically accomplished in less than seven milliseconds.[337]

This research made use of eight infrared tripod VICON T-20 cameras (Figure 4.2, left) with Nexus 1.8.5 software. The system captured 200 frames per second at 200 Hz. Passive retro-reflective markers with a diameter of 9.5 mm were used (Figure 4.2, right) and biomechanical outcomes were calculated according to the VICON Plug-in-Gait (VICON-PiG) model (using a validated lower body modified version of PiG). The VICON capture volume consisted of a 10-metre walkway (Figure 4.8). Gait events were detected for VICON outcomes using time-synchronised, floor-embedded force plates (Model FP9060-15, Bertec Corporation, Ohio, USA), each sized 0.4 m x 0.6 metres. The Bertec system's high-resolution provision of gait event timing renders it a suitable reference standard for gait event detection.[340]

Figure 4.2. The VICON T-20 infrared cameras used in the laboratory-based studies (left) and the passive retro-reflective markers used with the VICON system (9.5 mm diameter) (right).

4.10.2. The myoMOTION system (index system)

4.10.2.1. Description

The myoMOTION 3D IMC system (Noraxon USA Inc., Scottsdale, Arizona) is a fully portable IMC system comprising a combination of hardware and software which enables human motion capturing in three or six degrees of freedom. The system uses a receiver and compact Inertial Measurement Units (IMUs) (Figure 4.3 [A]), which are placed on body segments to provide 3D angular orientation data of that segment. The IMUs are small, lightweight and wireless and can be mounted on any segment of the body without using specific anatomical landmarks and

without restricting movement. Although individual IMUs are functionally identical, each is identified by a unique serial number. Thus, each IMU (serial number) can be assigned to any body segment during system configuration.

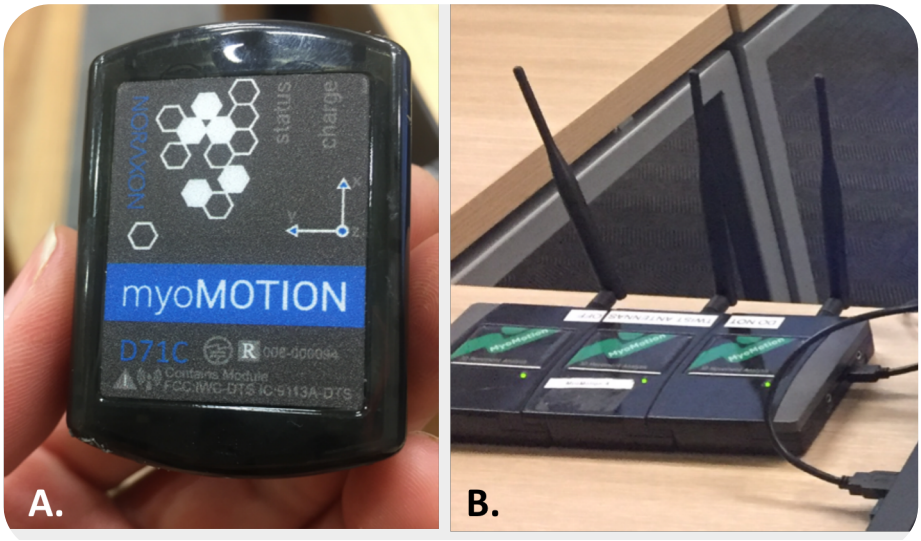


Figure 4.3. A: A single myoMOTION Inertial Measurement Unit (IMU). Dimensions: 37.6mm (length) x 52mm (width) x 18.1mm (height); 34 g (weight). B: The myoMOTION receiver.

IMUs are proprioceptive electronic devices incorporating a combination of miniaturised sensors: a 3D tri-axial gyroscope (measuring angular velocity or rate of rotation), a tri-axial magnetometer (measuring magnetic field vector), and a tri-axial accelerometer (measuring acceleration).[341,342] The IMUs utilise built-in sensor fusion algorithms to combine measurements from these sensors to measure the 3D rotation angles of each IMU in absolute space ("yaw-pitch-roll", also known as orientation or navigation angles). This concept can be visualised via an airplane flight manoeuvre (Figure 4.4). By measuring these 3D rotation angles, body segment tracking is achieved. Given that IMUs can track the Earth's gravitational and magnetic fields - which constitute universal reference signals[343] - an inertial north-east-up reference frame can be established anywhere; and since calibration of the capture volume is not required, a potentially unlimited capture volume is implied.[339]

Each body segment is mounted with an individual IMU. With proper calibration, the axes of the IMU local coordinate system represent a mutually orthogonal and normalised base that may constitute the segment technical frame, such that a network of two or more IMUs can be used to retrieve data from multiple body segments synchronously and track a multi-segment body relative to the same initial reference frame.[189]

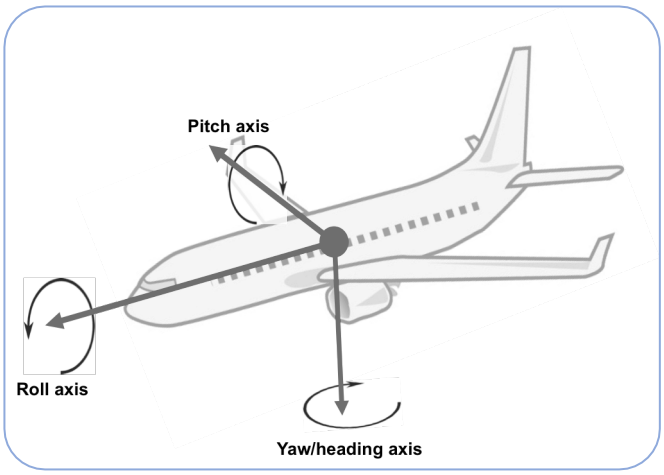


Figure 4.4. "Yaw-pitch-roll": representation of the three Inertial Measurement Unit (IMU) coordinate axes used to determine its own orientation in space, visualised as an airplane flight manoeuvre.

The motion-related signals (IMU data) are transmitted wirelessly by a small radio module to the Noraxon data acquisition and analysis software (myoRESEARCH 3.10.64 [MR3]) on the recording laptop. The software uses these data to construct a scaled full body model (Figure 4.5, top picture). Segment dimensions of the model are calculated using participant height (which is entered by the user into the software) to estimate anthropometric dimensions. The IMU data are transformed into segment kinematics within MR3 software using the biomechanical model provided (i.e. myoMOTION). The software converts the raw data into a readable format and provides the facility of exporting the data in the form of Microsoft Excel files (refer to Section 4.12: "Three-dimensional data acquisition and processing", for further

information). Movements can also be viewed in real-time in the software by means of a 3D skeletal avatar (Figure 4.5, bottom picture).

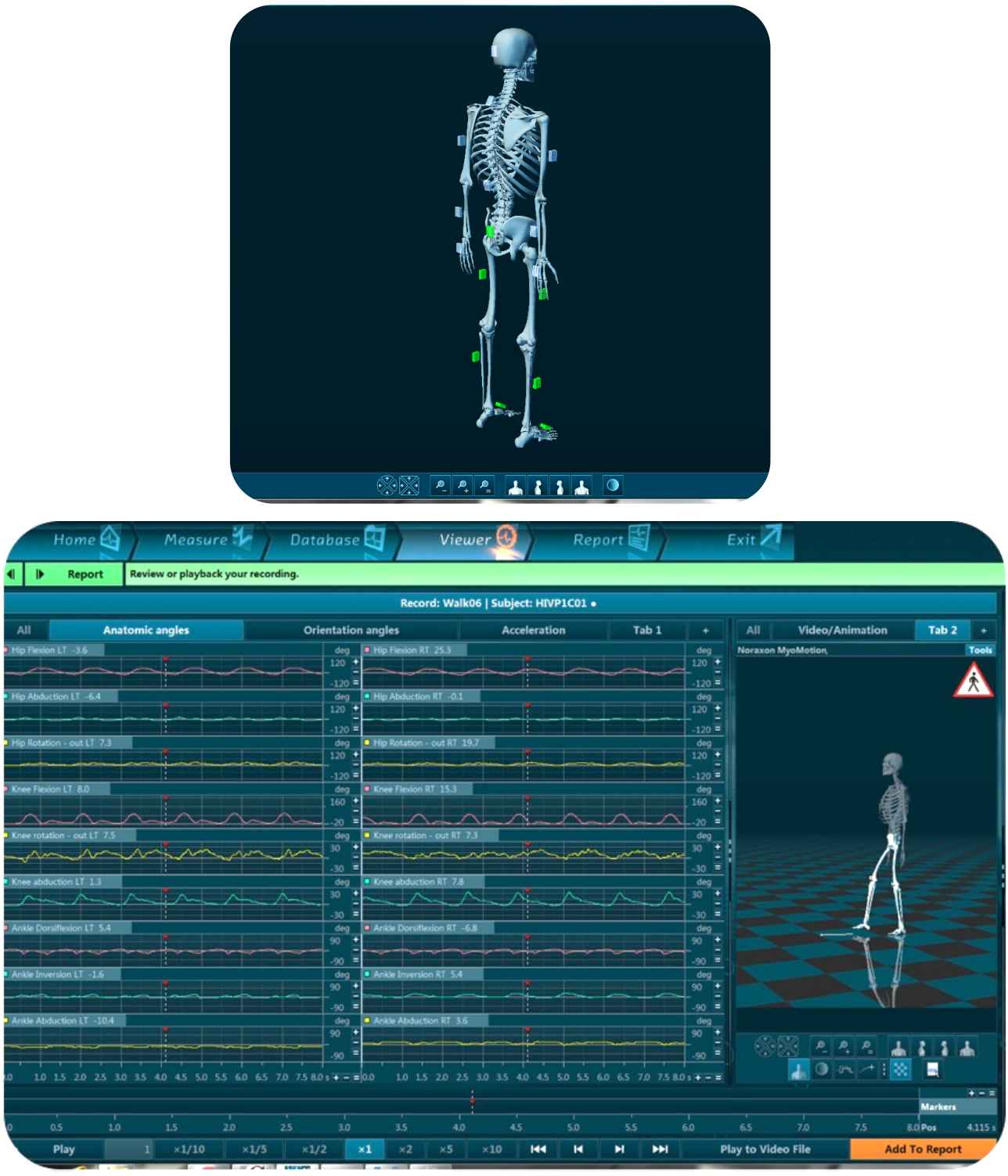


Figure 4.5. Top picture: The full body model viewed in MR3 software. Bottom picture: A screenshot showing the graphical interface of the MR3 software, including the skeletal avatar for the lower body model, which mimics the participant's movement in real time.

For this study, data were collected at 200 Hz using a seven-IMU lower body setup of the myoMOTION IMUs. Gait events were detected using an IMU-based algorithm provided by the MR3 system software.

4.10.2.2. MyoMOTION IMU technical performance

The wireless myoMOTION IMUs have a transmission range of 30 metres and sample rates of 100 Hz or 200 Hz (depending on the configuration). According to the manufacturers, the IMUs are capable of measuring angles with a static accuracy of ±0.4° and dynamic accuracy of ±1.2°.[344] The accuracy of the myoMOTION IMUs was also determined independently in the SU CAF motion laboratory during a technical pilot study prior to Study One. The results of this experiment demonstrated that static IMU tracking errors were 0.4°±0.2° (inclination) and 0.8°±0.4° (heading), while dynamic tracking errors were 0.9°±0.2° (inclination) and 2.0°±0.8° (heading).

Gyroscope tracking demonstrates good performance during short-term motions but is prone to a time-increasing drift over longer measurement periods. The reason for this is that IMU-measured signals are inherently characterised by an unpredictable accumulation of low-frequency random-walk noise during numerical integration.[189] IMU sensor-fusion algorithms are prone to fail after only a few minutes in the presence of interferences that are continuous and time-varying and thus detrimental to the correction of gyroscope drift errors.[339] Although commercial systems such as the myoMOTION come equipped with drift correcting sensor fusion algorithms, it is recommended that when collecting data over extended time periods, regular reset of the drift affecting the angular displacement should be done by means of recalibrating the system.[345]

4.10.2.3. Drift compensation and determination of kinematic joint angle estimation

Calculation of rotational angles and positions by the myoMOTION requires that values from the accelerometer, magnetometer and gyroscope be combined. Data from the accelerometer and magnetometer are used for initial positional determination, and the gyroscope's angular acceleration value is then integrated to calculate the angle. Any initial offset in the gyroscope's output will result in a gradually increasing amplitude drift, which distorts the motion information. On the other hand, accelerometers may suffer from noise during movement initiation or sudden directional changes. A robust sensor fusion algorithm (Kalman filter) compensates for

drift errors that might occur during the numerical integration process and combines various elemental sensor component axes readings into four-element vectors called quaternions.[345] By combining sensor outputs, the aforementioned shortcomings are to some extent resolved. This mathematical optimisation happens inside the IMU and not at the personal computer (PC)-level. The benefit of quaternions is that such data are able to represent all orientations without discontinuity, as opposed to Euler angles, which become limited in differentiating between some orientations when one of the angles has a value of 90° (called Gimbal lock).[339] Euler angles, which are geometrically more intuitive to interpret, may be calculated from quaternion data.[339] The quaternion data are automatically converted by the MR3 software into anatomical angles using a rigid body model with 16 joint segments (for the full body model) or seven segments (for the lower body model as used in this research). Each IMU's orientation angles and linear acceleration data are also recorded by the MR3 software, for later off-line use.

4.10.2.4. IMU orientation and position

As mentioned above, the information from a 3D accelerometer, gyroscope, and magnetometer is used to measure 3D rotation angles of each IMU in absolute space – which is then assumed to represent body segment orientation. In contrast to OMC, which provides positional information based on marker position and rate of change in position, the myoMOTION system directly measures the angular velocity of body segments via each IMU's on-board tri-axial gyroscope. Orientation is determined by mathematically integrating this angular velocity signal; that is, angular velocity of the IMU is integrated over time to provide the angular change from an initially determined angle.[346] The IMUs' on-board accelerometers are filtered simultaneously (at the same time as integration) such that the (downward) gravity vector is accurately separated from the IMU's linear acceleration vector. The drift accumulated during the gyroscope integration procedure is then corrected by using this gravity vector, while the linear acceleration is utilised as an almost direct metric of segment acceleration. Each IMU's position in the GCS (in relation to the calibrated starting point) is calculated at the IMU level by using measurements from both linear accelerometers and the gyroscopes used in calculating orientation.

4.10.2.5. Determining body segment orientation and position

The lower body myoMOTION biomechanical model used in this research consists of six joints connecting seven body segments. Each segment is considered to be a rigid unit with

interlinking joints; and a rigid attachment between IMUs and body segments are assumed. Therefore, the orientation of each IMU is assumed to represent the orientation of the segment that it is attached to. In contrast to these segment orientations, segment position requires some calculation with correction of drift errors and limitation of the freedom of movement of each IMU relative to its starting position. The myoMOTION assumes segments to form a kinematic chain with the pelvis as the segment of reference. Each subsequent proximal segment then forms the reference for the segment distal to it. Joint centre positions are calculated from the proximal segment reference position, the IMU orientation (representing the segment orientation) and the segment length (anthropometrically calculated by the MR3 segment using the inputted height data for each participant). Statistical constraints are applied to limit illogical joint movements such as large varus-valgus knee movement – which may occur due to the fact that body segments are not actually rigid units. For lower body angles the underlying Cardan rotation sequence adopted by the myoMOTION follows the recommendations of the International Society of Biomechanics (ISB). Considering the knee, the rotation sequence is thus flexion, abduction, and rotation. For this study, myoMOTION data were thigh-corrected, meaning that the axial rotation of the thigh segment was corrected to match the orientation of the shank, so that the resulting knee angles were always pure flexion (i.e. restricted to one degree of freedom).

4.10.2.6. Definition of myoMOTION body model segment axes and polarity

The myoMOTION system defines anatomical angles according to the rules and regulations of the medical neutral/zero method.[345] The underlying principle is that in a normal upright standing position, all joints are at the zero position, despite possessing an offset angle. An example is the ankle joint, which is normally in some degree of dorsiflexion (orientation) during upright standing, yet the neutral definition is 0°.

Each anatomical angle motion is comprised of positive or negative data in the angle curves. This polarity of movement is dependent on the plane of motion (Figure 4.6 [left] illustrates the three cardinal planes of movement, namely the sagittal, coronal and transverse plane). Starting from the neutral zero position, flexion at the knee joint, for example, causes positive signals, while extension causes negative signals (Figure 4.6, right).

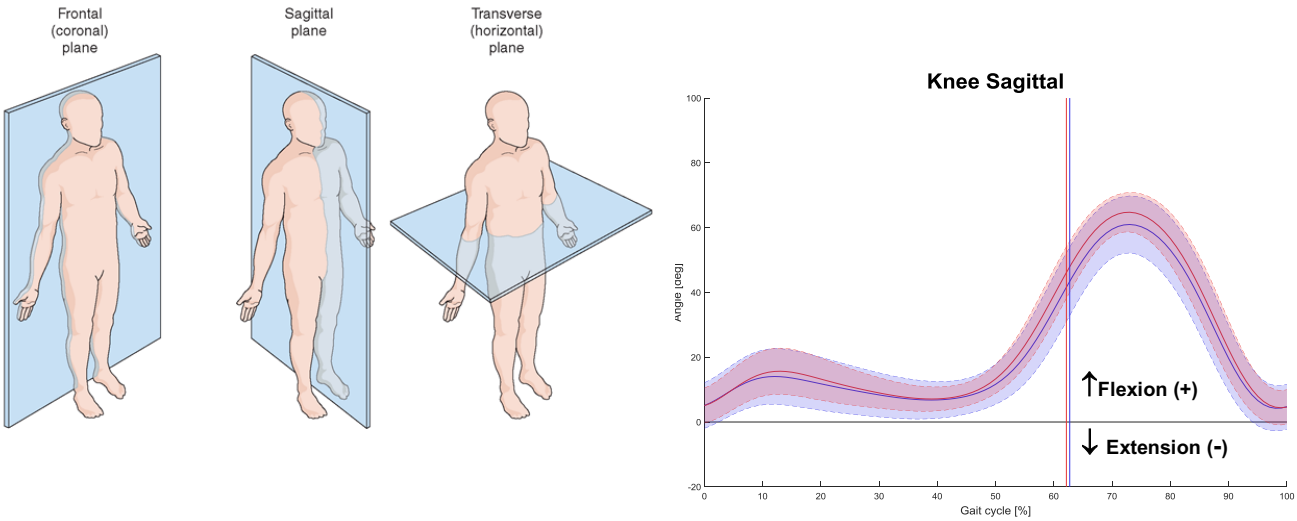


Figure 4.6. The three cardinal planes of human movement (left) and a representation of knee flexion/extension in the sagittal plane (right) (note the positive and negative angular degrees on the y-axis).

Although the myoMOTION biomechanical model is based on the standards for joint rotations sequences as set out by the ISB, some differences in conventions exist regarding polarity. For example, the myoMOTION defines positive angular values, depending on the joint/segment and axis/plane, as flexion, abduction, external rotation, dorsiflexion, and inversion; whereas the VICON-PiG convention defines positive directions as flexion (same as MR), adduction (opposite to MR), internal rotation (opposite to MR), dorsiflexion (same as MR) and inversion (same as MR). These issues were resolved by manually inverting ("flipping") the opposing angular polarities in myoMOTION output before comparison to VICON data. A description of all anatomical angle and polarity definitions, including those myoMOTION polarities that needed inversion to match the VICON definitions, is provided in Table 4.1.

Table 4.1. MyoMOTION/MR3 and VICON-PiG joint definitions and polarities. MR3 data were inverted in certain cases to comply with conventional VICON-PiG definitions.

Axis (plane)	MR positive direction	VICON-PiG positive direction		MR data inverted?
		Positive angle	Definition (PiG convention)	
X (sagittal)	Pelvic pitch	Pelvic tilt	A positive sign (up) corresponds to the normal situation in which the PSIS is higher than the ASIS.	No
Y (coronal)	Pelvic roll	Pelvic obliquity (up)	A negative pelvic obliquity value (down) relates to the situation in which the opposite side of the pelvis is lower.	No

Z (transverse)	Pelvic course (yaw)	Pelvic rotation (internal)	A negative (external) pelvic rotation value means the opposite side is in front (anterior).	Yes
X (sagittal)	Hip flexion	Hip flexion	A positive sign corresponds to the situation in which the knee is in front of the body (flexion).	No
Y (coronal)	Hip abduction	Hip adduction	A positive sign corresponds to an adducted (inwardly moved) leg.	Yes
Z (transverse)	Hip rotation (external)	Hip rotation (internal)	A positive sign corresponds to an internally rotated thigh.	Yes
X (sagittal)	Knee flexion	Knee flexion	A positive sign corresponds to a flexed knee.	No
Y (coronal)	Knee abduction	Knee adduction (varus)	A positive sign corresponds to varus (outward bend of the knee).	Yes
Z (transverse)	Knee rotation (external)	Knee rotation (internal)	A positive sign corresponds to internal rotation. If a tibial torsion value is present in the Session form, it is subtracted from the calculated knee rotation value. A positive tibial torsion value therefore has the effect of providing a constant external offset to knee rotation.	Yes
X (sagittal)	Ankle dorsiflexion	Ankle dorsiflexion	A positive sign corresponds to dorsiflexion.	No
Y (frontal)	Ankle Inversion	Ankle adduction (inversion)	Different nomenclature between systems/models confirmed using MR3 software. Frontal plane - adduction corresponds to internal.	No
Z (transverse)	Ankle abduction (external rotation)	Ankle internal rotation	A positive sign corresponds to internal rotation. Different nomenclature between systems/models were confirmed using MR software. Transverse plane - adduction is internal.	Yes

VICON definitions from official VICON motion systems online resources.[347,348]
Due to differences in terminology between systems/models, directions corresponding to nomenclature were verified by simple practical movement experiments using IMUs and MR3 software.

4.10.2.7. TSP determination by the myoMOTION

The gait events of initial contact and toe-off were detected by the myoMOTION using an IMU-based contact detection algorithm provided by the MR3 software. The algorithm utilises foot angular velocity as well as acceleration measurements from the foot-mounted IMU to identify periods when the foot is in contact with the ground. TSPs are subsequently calculated in MATLAB software (R2017a, MathWorks) from each foot-contact signal.

4.11.Study procedures

The following study procedures were followed for both studies One and Two, unless specifically stated otherwise.

4.11.1. Laboratory preparation and system calibration

Standard laboratory protocol was followed using a VICON T-wand for dynamic VICON calibration, with a laboratory technician moving the wand in sweeping movements while walking through the capturing volume. The software then calculated the cameras' motion detection ability inside of the capturing volume. Subsequently, the cameras' accuracy in detecting the marker orientation relative to one another and within the capturing volume was determined: system-marker orientation was undertaken by placing the T-wand on the force plate system, which was synchronised with the VICON.

4.11.2. Participant preparation and clinical assessment

Participants were welcomed and introduced to the laboratory and the logistics of the subsequent testing procedures. Each participant was scheduled for a single test visit and a maximum of four participants were tested per day (both studies). For Study Two, all participants to be tested on a specific day were transported together in a minibus between Worcester and Tygerberg campus. Participants were provided with beverages, a light lunch and magazines and relaxed in a private waiting room in the physiotherapy clinic adjacent to the motion laboratory while testing was conducted on one participant at a time.

Basic sociodemographic information and medical history was recorded for each participant. For EndoAfrica participants (Study Two), data were extracted from the overhead study, along with laboratory results confirming HIV status. HIV-specific data extracted from the EndoAfrica database included: CD4 cell count, viral load, date of HIV diagnosis and antiretroviral treatment history, in order to obtain a descriptive disease profile of PLHIV in which validity and reliability was determined.

Women were tested in sleeveless sports tops and shorts, and men wore shorts only, to obtain accurate marker and IMU placement and optimal visibility. Participants remained bare footed during physical evaluation, calibrations and all subsequent motion analysis. A standardised physical assessment was conducted on each participant at the start of the data collection session: Lower limb joint range of motion (ROM) was screened (Section 4.11.2.1) and

essential VICON-specific anthropometric measurements were taken (height, weight, leg length from ASIS to medial malleolus, knee- and ankle width) (Section 4.11.2.2), as required by the PiG model.

4.11.2.1. Lower limb range of motion screening

In addition to subjectively inquiring about joint restrictions hampering the participant's functional gait (which constituted an exclusion criterion as stated previously), the lower limbs of each participant were briefly screened for gross joint range discrepancies using a manual international standard goniometer with a 360° scale marked in one-degree increments (Model G300, Whitehall Manufacturing Hydrotherapy and Health Care Products, CA, USA). Joint ranges of motion (ROM) specifically screened included the major drivers of gait in a forward direction (hip flexion and extension, knee flexion and extension, ankle dorsi- and plantarflexion; any other obvious ROM restrictions or hypermobility noted for a specific participant were also recorded.

4.11.2.2. Anthropometric measurements

Height was measured barefoot by having the participant stand in the anatomical position with their feet together, heels, buttocks and back against a wall, looking straight ahead and with the head in the Frankfurt horisontal plane (achieved when the orbitale is in the same horisontal plane as the tragion).[349,350] A wall-mounted calibrated stadiometer was used to record height to the nearest 0.5 centimetres (cm).

Body weight was measured to the nearest 0.1 kilogram (kg) using a Safeway electronic body scale (maximum capacity of 150 kg). Participants were measured barefoot and wearing light clothing, with feet equally spaced on the scale platform.

BMI was calculated as:

$$BMI = \frac{(weight\ in\ kilograms)}{(height\ in\ metres)^2}$$

Leg length was measured in supine from the ASIS (most inferior aspect) to the medial malleolus (most inferior aspect) via the knee joint and with the leg resting in neutral, using a measuring tape. Measurements were made to the nearest 0.1 cm, and left and right sides were averaged.[351] Knee joint width between lateral and medial joint lines at the flexion axis was measured using calipers and to the nearest 0.1 cm, with the participant lying supine. Ankle width was also measured in supine, using calipers, from the most medial point of the

medial malleolus to the most lateral point of the lateral malleolus and recorded to the nearest 0.1 cm.

4.11.3. Marker/IMU placement

Acting as the single rater of the index system in both studies, being a registered physiotherapist with prior experience with the VICON system (from MSc research) and having completed the VICON Optical Motion Capture Workshop and myoMOTION Training Workshop offered by the SU CAF Training Initiative (2015), the researcher (PhD candidate) performed all marker and IMU placements throughout the studies.

The markers and IMUs were placed on the participant simultaneously to enable concurrent measurements by both systems for validity determination. Prior to placement, the relevant skin areas were wiped with surgical alcohol to facilitate good contact between the markers/IMUs and the skin. Twenty passive retro-reflective markers (9.5 mm diameter) were placed on anatomical landmarks according to a validated modified lower body PiG model provided by the VICON software (Nexus 1.8.5). Using medical grade double-sided adhesive tape, the markers were placed on the heels (calcaneus, at the same height above the plantar surface of the foot as the toe marker), medial malleoli, lateral malleoli, second metatarsals (on the mid-foot side of the equinus break), shanks (using wands, along the alignment of the ankle flexion axis), tibial tuberosities, lateral knees (on the flexion/extension axis), medial knees (on the flexion/extension axis), lateral thighs (lower lateral one third surface), anterior superior iliac spines (ASIS's) and posterior superior iliac spines (PSIS's) (Figure 4.7). These markers were not removed during any trials and thus could not introduce bias due to variation in placement.

Seven IMUs were placed on the various lower limb segments according to the rigid lower body model; taking care to not interfere with the reflective markers. For the lower body setup of the myoMOTION, the IMUs were placed on the pelvis (posteriorly on the sacral surface), thighs (lateral attachment to the lower quadrant of the segment, i.e. the area of lowest muscle belly displacement during walking), shanks (anteromedial surface of the tibia), and feet (dorsally and sufficiently proximal to the equinus break to avoid excessive IMU motion) (Figure 4.7). IMUs were attached with a fixation strap (pelvis), elasticated Velcro straps (thighs and shanks) (all these straps are provided standard along with the myoMOTION) and double-sided tape, firmly reinforced using elastic adhesive bandage (feet). These placements were done in such a manner that no movement restrictions were imposed on the participants. All markers/IMUs were checked by the researcher and the laboratory technician throughout measurement procedures to ensure that they remained in place.

Although IMUs distal to the pelvic IMU can be mounted to any position of the selected body segments, standardised guidelines were followed in this project to promote quality and fidelity of the collected data:

- Areas susceptible to excessive soft tissue movement (e.g. muscle bellies, where muscle contraction would most likely move the IMU) and bony prominences (where uneven surface attachment would cause IMU movement) were avoided. IMUs were thus placed on flat surfaces of the relevant body segments with the least muscle tissue between the bone and sensor.
- IMUs were applied symmetrically on both sides of the body to ensure measurement under the same conditions.
- Medical-grade double-sided tape was used to secure the contact area of the straps containing the IMUs and prevent “tilting” of the IMU with regards to the body surface.

The thigh poses a particular threat to IMU motion due to an increased risk of soft tissue artefact (STA) – which may affect 3D knee angle measurements. After troubleshooting different IMU placement options using two pilot participants (not included as part of the analysed participants in any of the primary studies), it was decided that the best data would be collected by securing the thigh IMUs to the lateral aspect of each thigh (Figure 4.7).

Figure 4.7. Standardised N-pose and positioning of reflective markers and IMUs. Twenty passive retro-reflective markers were placed on the relevant anatomical landmarks. IMUs were attached with a fixation strap (pelvis), Velcro straps (thighs and shanks) and double-sided adhesive tape, and firmly reinforced using elastic adhesive bandages (not shown here) over foot IMUs. Standardised instructions were provided by the rater, namely to (1) stand straight with arms crossed, (2) vertically align centers of the hip-, knee- and ankle joints (to position feet hip-width apart), (3) place feet perfectly parallel and facing forward (key criterion) and (4) have the pelvis facing directly forward in the same direction as the feet (key criterion). Participants were instructed to remain static until completion of the ~15s system calibration (indicated by an audio signal).

4.11.4. Practice trials

Participants were allowed sufficient time to become familiar with the testing procedures and gait trials and were explicitly instructed to walk “as normal as possible”. To familiarise participants to the feeling of walking with the IMU/markers fixated to their bodies, practice trials were performed along the capture volume, noting specific starting positions for optimal force plate foot strikes, and until the researcher was satisfied that the participant assumed a relaxed,

normal gait. To avoid any potential force-plate targeting, participants were instructed to look ahead and focus on the laboratory wall in front of them at eye level.

4.11.5. Biomechanical model calibration

4.11.5.1. VICON-PiG

After the practice trials, a static anatomical VICON-PiG calibration was performed with the participant standing on the force plate according to standard laboratory protocol (once-off per participant and prior to myoMOTION calibration; therefore, ferromagnetic interferences were not a concern). Each calibration trial was reconstructed by the laboratory technician to produce 3D reconstructions of all markers used. The reconstructed 3D markers were associated with marker labels from the modified PiG labelling model, allowing manual labelling of the markers and construction of a participant image. To allow the PiG model to calculate key parameters, all markers placed on the participant were included in the VICON skeleton template, which was calibrated to the VICON skeleton file created for each participant. All trials were reconstructed to graphically represent participants, and were subsequently rechecked for accuracy of the labelling of the anatomical marker positions.

4.11.5.2. MyoMOTION

The myoMOTION model was calibrated as per the user guide instructions by having the participant remain stationary in a neutral reference posture during calibration (Figure 4.7), in order to establish the local coordinate system and provide a reference angle on which to base the collected kinematic data. The calibration pose was arranged as accurately as possible to minimise subsequent measurement errors. Calibrations were performed on a 30 cm-high wooden platform, minimising exposure to potential floor-based magnetic distortions, and with the participant facing in the same direction as the subsequent walking trials. Substantial attention was paid to postural setup and standardised instructions were provided (see Figure 4.7 caption).The researcher inspected the N-pose in three planes, enforcing neutral joint angles. MyoMOTION calibration was then initiated, requiring the participant to remain static for about 15 seconds (a successfully completed calibration procedure is indicated by system by emitting an auditory signal).

The myoMOTION system allows the calibration data to be used for repeated measure series of data collection (using the option “Use last calibration” in the software); however, frequent re-calibration of sensors within test series is recommended to avoid drift over time, and

therefore the system was recalibrated each time in-between gait trials (as would be the case in the field study as well).

4.11.6. Experimental protocol and data collection

Figure 4.9 outlines the procedures for the gait and N-pose validation and reliability studies. The recording protocol lasted approximately 35 to 40 minutes per participant.

4.11.6.1. N-pose

VICON measurements were recorded concurrently during myoMOTION calibrations. A quality check was performed before initiating each calibration (activating the “Calibrate” command in the software) to ensure that no VICON markers were occluded, and that no ferromagnetic interference was present with regards to the IMUs (indicated by IMUs turning red on the operating screen). The recorded data were used in VICON Nexus software to define the static kinematic angles maintained during the calibration pose, according to the PiG model. MyoMOTION postural measurements are not available during calibration; however, myoMOTION joint/segment angle values of zero in all planes were used for later analysis (Study One) since the system assumes these for the reference posture. VICON-recorded data of the N-poses were recorded in both studies, but only analysed in Study One (for intra-rater accuracy and repeatability) while being used for offset removal between systems in both studies. Standardised instructions for the N-pose setup are briefly summed in the caption of Figure 4.8.

4.11.6.2. Gait

The VICON capture volume consisted of a straight, level 10-metre walkway with the force plate system embedded midway (Figure 4.9). Participants started walking approximately one metre before a taped line on the floor and ended after crossing a second line; myoMOTION recordings were confined to the same distance by manual start and stop. Each participant performed six myoMOTION-recalibrated gait trials (one N-pose before each trial). Gait trials immediately followed myoMOTION calibrations. Participants walked barefoot, and at a usual-paced (comfortable self-selected) gait speed to imitate performance in a clinical setting. Six clean force plate strikes were needed, with alternating feet (three strikes per side). Participant were thus instructed to alternate the starting foot with each trial. A gait trial was deemed successful if the participant’s entire landing foot made contact with at least one of three force-plates and if they did not target the force-plate by looking down at it or by noticeably changing their stride length. The intercepted gait trials were performed in the same direction each time

and after each trial, the participant returned immediately to the wooden platform for the next calibration. Figure 4.10 shows the graphical interfaces of each system, viewed for a gait trial.

Figure 4.8. The laboratory space where both validity and reliability studies were conducted.

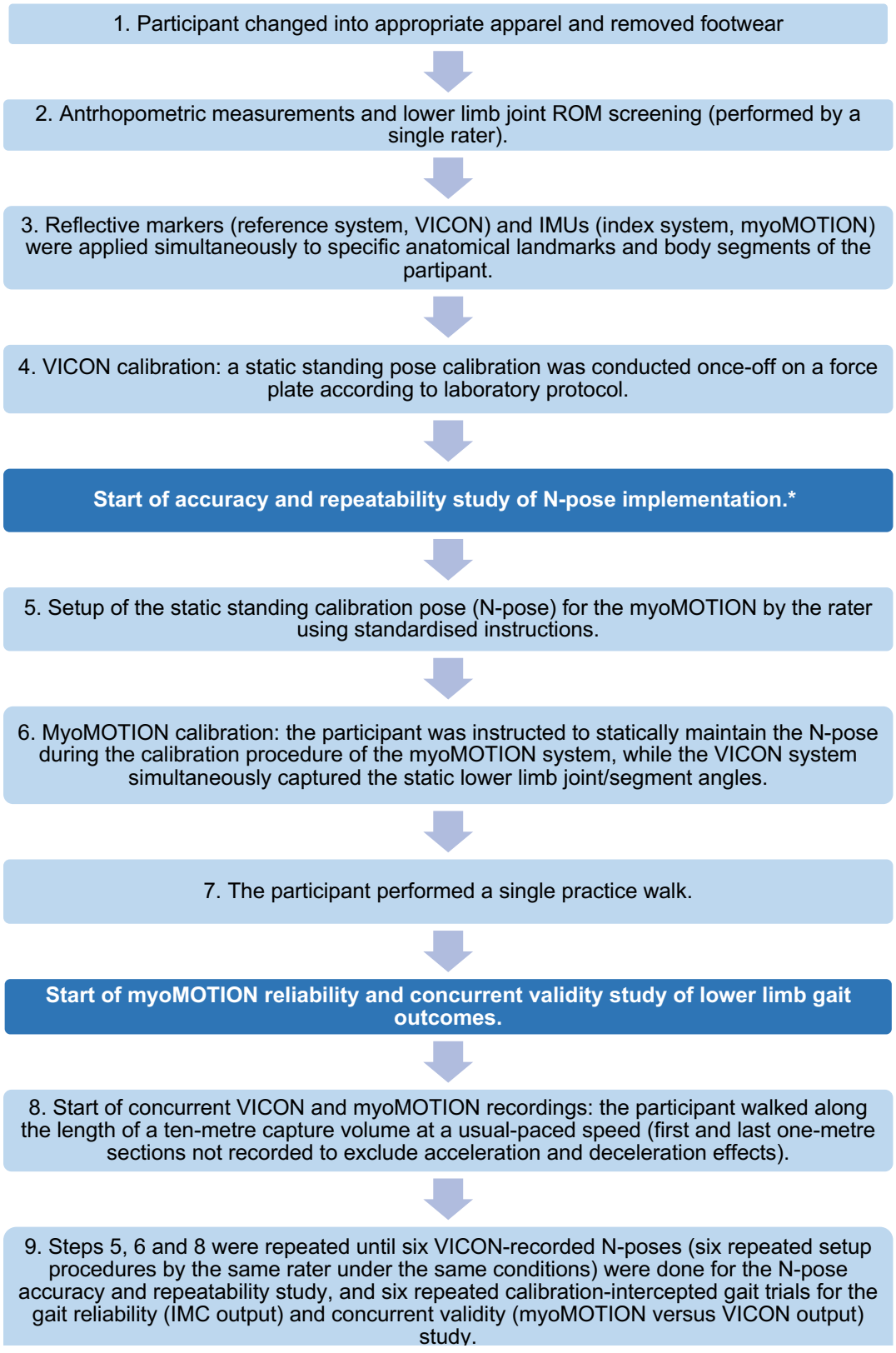


Figure 4.9. Data collection procedures per participant (Studies One and Two). *N-pose data were recorded using VICON in both studies, but only analysed in Study One (for intra-rater accuracy and repeatability) while being used for offset removal between systems/models in both studies.

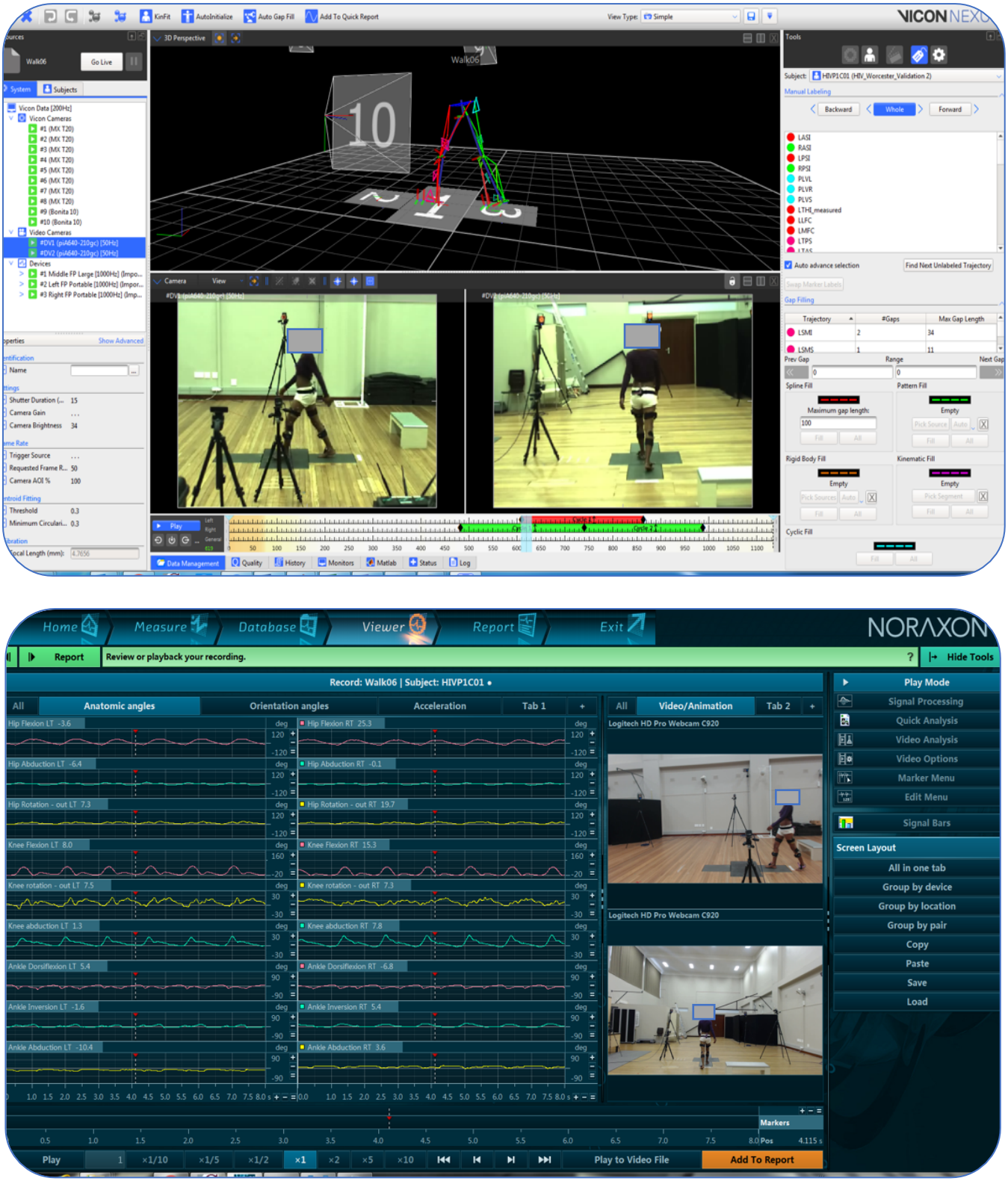


Figure 4.10. Screenshots during gait recordings to show the graphical interface for each system (top = VICON Nexus; bottom = myoMOTION MR3).

4.12. Three-dimensional data acquisition and processing

Data processing was performed by a qualified neuromechanics laboratory analyst, in continuous close consultation with the researcher. Pre-processing of individual static N-pose trials (recorded by VICON during myoMOTION calibration) and gait trials was done in Nexus software.

Each static VICON calibration trial (performed only once per participant for the purposes of VICON calibration), as well as individual gait trials, was reconstructed by the laboratory technician, using a validated modified lower body marker set contained in the VICON skeleton template. By manually labelling the markers, the technician created an image of the participant, which was then screened for accuracy of the labelling of the anatomical markers. Gaps in marker trajectories were inspected and filled using the Woltring gap filling algorithm (Quintic spline; mean square error setting of 20mm^2) built in to Nexus software. If gaps remained in the marker trajectories (due to poor visibility or occlusion of markers) further, manual gap filling was done.

Gait events (foot contact and toe-off) were inserted using the force plate data and auto-correlated to the rest of the trial where necessary. A threshold of 20 Newtons (N) was used to determine the points of foot contact and toe-off. If the events are not repeatable or were inaccurately correlated, they were manually corrected within Nexus software using time-synchronised video.

The PiG model was then executed and the model outputs determined. Joint/segment kinematics and calculation of joint motion were obtained from the VICON-PiG model using the standard dynamic PiG operation in the VICON Nexus software, which determines hip joint centres relative to the associated embedded coordinate system origin using the Davis equations[352] (i.e., the hip centre location relative to the origin of the pelvic embedded coordinate system, which is located midway between the ASIS markers).[352] Knee axis estimation was performed by optimising the thigh-rotation offset parameter during gait[353] and ankle axis estimation by determining the shank-rotation offset parameter during the static N-pose trial using medial and lateral malleolus markers. These data were filtered using a 4th order zero-lag low pass Butterworth filter with a cut-off frequency of 6 Hz. The Bertec force plate data were filtered at 100 Hz with the same filter.

The motion related signals from the myoMOTION were transmitted wirelessly to the MR3 software on a recording laptop (200 Hz). The software automatically filters the raw data using a robust fusion algorithm (Kalman filter) optimised for IMU data. IMU angular orientation is estimated by a combining the elemental sensor component axes readings into four element quaternion values. As mentioned before, these calculations are performed at IMU-level. Thus, pre-processing was not needed, but data were corrected for magnetic drift (distortion) on the foot, shank and thigh segments. MyoMOTION gait events were also determined within the software (using the built-in algorithm). Raw myoMOTION data were filtered using a 4^{th} order zero-lag low pass Butterworth filter with a cut-off frequency of 6 Hz, to attenuate any noise within the signals.

The data recorded in MR3 (myoMOTION) were exported to single .csv files (for each trial). The data recorded in Nexus (VICON) were saved as .c3d files. All data were subsequently imported into MATLAB software (R2017a, MathWorks), a high-performance software for processing and analysis. In cases where a gait trial contained more than one complete and valid gait cycle for one or both legs, only the gait cycle for each leg judged to contain the best data quality was retained for analysis, discarding the rest of the gait cycles in the trial. Data segmentation was subsequently performed, which involved using the cyclical gait events, defined by the foot contact and foot off events, to segment trial data into cycles normalised in time to 101 data points from initial contact (0%) to ipsilateral initial contact (100%) at time intervals of 1%.

Prior to determining myoMOTION outcomes, the relevant data were inverted (“flipped”) according to the positive definitions of each joint/segment motion (as defined in Table 4.1). Model-adjustment of myoMOTION data was also done at this point. Data outcomes were then determined using custom analysis scripts, including the construction of visualisations in MATLAB that can be exported to image files or MS Word documents. Finally, using a macro routine, all outcomes were exported to MS Excel for further statistical analysis.

4.12.1. Offset correction of myoMOTION data

For model-corrected comparisons, a second myoMOTION data set was created wherein gait kinematics were adjusted by the Euler angle offset measured by VICON during myoMOTION calibration. The myoMOTION data were adjusted using the static standing trials recorded between each walking trial in Nexus. This was done at the same stage as data inversion. The angles of each joint/segment (in each plane) in the static trials were considered the neutral

(natural standing posture) and were used to offset the myoMOTION data (shifting the data to the same neutral joint/segment positions as for the VICON-PiG model). This was done using the simple equation for each joint/segment and plane:

```
offset_angle = mean angle in static trial
MM_angle_adjusted = MM_angle(whole cycle) + offset_angle
```

The correction was applied slightly differently for pelvis rotation and foot progression heading (third plane) angles because of their relationship with the global co-ordinate system and given the limitations of IMUs (inability to measure absolute skeletal position kinematics).

This approach is less accurate than using matrix mathematics to reorient anatomical frames of the myoMOTION model using VICON data. However, the matrix approach would not have allowed for an evaluation of the commercial myoMOTION model and calibration, which were being validated for the current research. In addition, access to the source code was not available. The Euler angle approach can be considered conservative for validation purposes, as it would presumably remove model differences less effectively. Therefore, if the Euler angle offset method was to produce sufficiently valid myoMOTION comparison results, the matrix approach would most likely have produced slightly better (not worse) results.

Since time-shifts in the gait cycle data (due to differences in gait event detection and thus segmentation) could lead to comparison errors, a third myoMOTION dataset was created (in Study One only) wherein the model (angular offset)-corrected gait kinematics were adjusted for time-segmentation differences due to between-system gait event detection differences. MyoMOTION time-series data from the biomechanical model were time-synchronised to OMC data offline by aligning a common event (VICON foot contact event):

```
offset_angle = vicon_angle(@ Vicon foot strike) MM_angle(@ Vicon
foot strike)
MM_angle_adjusted = MM_angle(whole cycle) + offset_angle
```

The myoMOTION data were thereafter segmented and time-normalised using VICON events to allow for comparison of the systems' data independent of event detection error.

4.12.2. Outcome angles and TSP parameters

As a first exploration into system performance, Study One compared the average angular values achieved during the N-pose setup, as well as the average arithmetic means of kinematic gait waveforms commonly included in a gait analysis. For the knee and ankle, secondary angles (coronal and transverse planes) were not analysed for gait as these outcomes are less reliable even using OMC, hampering correct interpretation of the kinematics[354] (especially knee ab-adduction and rotational data are associated with poor signal-to-noise ratios).[352]

Calibration pose data were also collected in Study Two, but not analysed (as intra-rater repeatability for setting up these poses using standardised instructions was already confirmed in Study One). These data were thus only used to correct offset error (as in Study One) for comparison of raw and corrected system outputs. Study Two compared discrete kinematic angles and ROMs considered clinically relevant in discriminating elderly and/or fall-prone gait, so as to confirm the measurement error of the myoMOTION for these outcomes which were to be collected in-field in the subsequent cross-sectional field study. In addition, selected TSPs were assessed for concurrent validity and reliability.

The following kinematic waveforms, presented in Table 4.2 below, were calculated and analysed in Study One, and used for extraction of selected clinically relevant discrete angles and ROMs for Study Two as well as the cross-sectional field study (Chapters 7 to 8).

Table 4.2. Kinematic waveforms extracted and analysed in Study One.

Anatomical angle	Description	Polarity
Pelvic tilt	Pelvic motion in the sagittal plane (X)	Anterior tilt (+); posterior tilt (-)
Pelvic obliquity	Pelvic motion in the coronal plane (Y)	Upward obliquity (+); downward obliquity (-)
Pelvic rotation	Pelvic motion in the transverse plane (Z)	Internal rotation (+); external rotation (-)
Hip flexion/extension	Hip motion in the sagittal plane (X)	Flexion (+); extension (-)
Hip abd/adduction	Hip motion in the coronal plane (Y)	Abduction (+); adduction (-)
Hip rotation	Hip motion in the transverse plane (Z)	Internal rotation (+); external rotation (-)

Knee flexion/extension	Knee motion in the sagittal plane (X)	Flexion (+); extension (-)
Knee abd/adducton[a]	Knee motion in the coronal plane (Y)	Adduction (+); abduction (-)
Knee rotation[a]	Knee motion in the transverse plane (Z)	Internal rotation (+); external rotation (-)
Ankle dorsi/plantarflexion	Ankle motion in the sagittal plane (X)	Dorsiflexion (+); plantarflexion (-)
Foot progression[a]	Foot motion in the transverse plane (Z)	

[a]*These angles were not included in the gait analysis.*

4.12.3. Definition and extraction of kinematic key events

The kinematic angles extracted from the relevant software for each participant consisted of time-varying gait curves normalised to 101 data points, as presented in Table 4.2 above. Since no data exist regarding instrumented gait analysis in PLHIV, for Study Two (this chapter and Chapter 6) and the field study (Chapters 7 to 8), key events and phases from each kinematic curve were selected based on data from previous studies in the elderly and fallers (reviewed in Chapter 2). A large number of variables were included to facilitate data exploration in the validation and reliability studies as well as in the cross-sectional field study. This approach has previously been used by a number of 3D gait analysis studies, particularly in populations whose gait characteristics had not previously been assessed in detail using instrumented analysis.[355,356]

Extraction of the key points from the time-normalised average of each assessment was performed using a customised routine in MATLAB, based on key event definitions listed in Table 4.3 and key phase definitions in Tables 4.4. Table 4.5 lists and defines the kinematic angular outcomes used in the second validation and reliability study and considered for the cross-sectional field study. The definitions used for gait analysis outcomes were based on conventions as per Whittle's Gait Analysis.[201]

Table 4.3. Key events used to define kinematic outcomes, based on Whittle's classification of the gait cycle.[201]

Event	Abbreviation	Description	Definition for use in MR
Initial contact 1	IC1	First contact of the foot with the ground (marks beginning of loading response)	Defined by myoRESEARCH software (MR3)
Toe-off	TO	Point when the foot breaks contact with the ground	Defined by MR3
Heel rise	HR	Point when heel starts to lift from ground (marks transition from mid-stance to terminal stance)	Defined at maximum knee extension during stance
Opposite toe-off	OTO	Point in stance of the ipsilateral limb when the contralateral limb begins swing (marks the end of the first double support period and start of mid-stance)	Defined by MR3
Opposite initial contact	OIC	Point in stance of the ipsilateral limb when the contralateral limb begins stance (marks end of single support period and start of pre-swing/second double support)	Defined by MR3
Feet adjacent	FA	Point when the swinging leg passes the stance leg and the feet are side-by-side (separates initial swing from pre-swing)	Defined at maximum knee flexion during swing
Tibia vertical	TV	Point when the tibia of the swinging leg becomes vertical (separates mid swing and terminal swing)	Defined using the shank angle in MR3 (manually checking for verticality during swing)
Initial contact 2	IC2	Next initial contact of the same foot, marking the end of the GC	Defined by MR3

Table 4.4. Delamination and definition of gait phases, including defining events.

Phase or sub phase	Definition	Defining events
Gait cycle (stride)	Constitutes the basic unit of gait and is defined as the time period between two successive occurrences of one of the repetitive events during walking; by convention foot contact with the ground	IC1 to IC2
Stance phase		IC1 to TO
Loading response/first double support	Period of weight acceptance, starting from initial contact to opposite toe-off. Corresponds to first double support phase.	IC1 to OTO
Mid-stance	The first half of single support, lasting from opposite toe-off to heel rise of ipsilateral foot.	OTO to HR
Terminal stance	The second half of single support, lasting from ipsilateral heel rise to opposite initial contact.	HR to OIC
Pre-swing/second double support	The second double support phase, lasting from opposite initial contact to ipsilateral toe-off.	OIC to TO
Swing phase		TO to IC2
Initial swing	Period from toe-off to instant when swing leg is adjacent to stance limb.	TO to FA
Loading response and mid-stance periods		LR (begin) to MSt (end)
Mid-stance and terminal stance periods		MSt (begin) to TSt (end)
A1	Portion of the GC corresponding to the A1 power phase of the ankle: a region of negative power, corresponding to eccentric plantar flexor activity at the ankle during midstance and terminal stance	Maximum ankle plantarflexion in MSt to maximum ankle dorsiflexion in TSt
A2	Portion of the GC corresponding to the A2 power phase of the ankle: a region of positive power, corresponding to the concentric burst of propulsive plantar flexor activity during pre-swing.	HR to TO

K1	Portion of the GC corresponding to the K1 power phase of the knee: a region of negative power, corresponding to eccentric knee extensor activity at during loading response.	IC1 to maximum knee flexion in stance
K2	Portion of the GC corresponding to the K2 power phase of the knee: a region of positive power, corresponding to concentric knee extensor activity during midstance. This is followed by a period of negligible joint power during that period of time when the ground reaction force stabilizes the knee in extension.	Maximum knee flexion in MSt to maximum knee extension in TSt
K3	Portion of the GC corresponding to the K3 power phase of the knee: a region of negative power, corresponding to eccentric activity in the rectus femoris during pre-swing. At normal or slightly faster walking speeds, rectus femoris controls knee flexion.	Maximum knee extension in TSt to maximum knee flexion in swing
H3	Portion of the GC corresponding to the H3 power phase of the hip: a region of positive power, corresponding to concentric activity in the hip flexors during pre-swing and initial swing. Sometimes called "pull off", this is the muscular system's second largest contribution of propulsive power during the gait cycle.	Maximum hip extension in stance to maximum hip extension in swing

Abbreviations: A1/A2 = A1/A2 power phases of ankle; FA = foot-adjacent; GC = gait cycle; H3 = H3 power phase of hip; HR = heel rise; IC = initial contact; K1/K2/K3 = K1/K2/K3 power phase of knee; LR = loading response; MSt = mid-stance; ROM = range of motion; TO = toe-off; TS = terminal stance.

Table 4.5. Kinematic outcomes used in the second validation and reliability study and the cross-sectional field study.

Joint/segment	Discrete angle/ROM	Corresponding GC event/phase
Pelvis	Pelvis tilt ROM during the GC	GC
	Pelvis obliquity ROM during the GC	GC
	Pelvis rotation ROM during the GC	GC
	Peak anterior pelvis tilt angle during the GC	GC
	Pelvis rotation angle at initial contact	IC1
Hip	Hip flexion ROM during the GC	GC
	Hip internal rotation ROM during the GC	GC
	Hip flexion ROM during loading response	LR
	Hip flexion ROM from pre-swing to initial swing	H3
	Hip abduction ROM during mid-stance	MSt
	Hip adduction ROM during loading response	LR
	Peak hip joint flexion during stance	Stance
	Peak hip joint flexion during swing	Swing
	Hip joint flexion angle at initial contact	IC1
Knee	Knee flexion ROM during the GC	GC
	Knee flexion ROM during stance	K1
	Knee extension ROM, mid-stance to terminal stance	K2
	Knee flexion ROM, stance to swing	K3
	Knee joint flexion angle at initial contact	IC1
	Peak knee joint flexion during stance	Stance
	Peak knee extension angle during stance	Stance
	Peak knee flexion angle during swing	Swing
Ankle	Ankle dorsiflexion ROM during stance	A1
	Ankle plantarflexion ROM, heel rise to toe-off	A2
	Ankle dorsiflexion ROM during swing	Swing
	Peak ankle plantarflexion during the GC	GC
	Ankle dorsiflexion angle at initial contact	IC
	Ankle plantarflexion angle at toe-off	TO

Abbreviations: A1/A2 = A1/A2 power phases of ankle; GC = gait cycle; H3 = H3 power phase of hip; HR = heel rise; IC = initial contact; K1/K2/K3 = K1/K2/K3 power phase of knee; LR = loading response; MSt = mid-stance; ROM = range of motion; TO = toe-off; TS = terminal stance.

For Study Two and the field study, but not for Study One (relevant MR3 algorithms were under development at the time), TSPs that have been reported to be of clinical relevance in discriminating elderly and fall-prone gait were included in the analyses. For both systems, TSP data were normalised to leg length into dimensionless quantities as recommended by Hof.[357] This scaling of gait data is often used to minimise the inter-participant variation by correcting as much as possible for differences in stature, which directly influences parameters.[358] According to Hof[357]:

$$normalised\ length = \frac{length}{l_0}$$

$$normalised\ speed = \frac{speed}{g \times l_0}$$

where g is acceleration due to gravity (9.81m/s^2) and l_0 is leg length (ASIS to medial malleolus). These normalisations resulted in the non-dimensional variables included in Table 4.6.

Table 4.6. TSPs extracted from MATLAB for both measurement systems.

Parameter	Description	Units
Spatial parameters		
Step length	Distance between corresponding successive initial contact of opposite feet, measured parallel to the direction of progression for the ipsilateral stride	cm
Normalised step length	Dimensionless normalisation of step length to leg length: $step\ length \times \frac{1}{l_0}$	Dimensionless
Stride length	Distance travelled during one stride (or GC); measured as the length between ipsilateral successive initial contact of the foot	cm
Normalised stride length	Dimensionless normalisation of stride length to leg length: $stride\ length \times \frac{1}{l_0}$	Dimensionless
Temporal parameters		
Stance time	Time period when the foot is in contact with the ground	Seconds
Step time	Time taken for one step, measured from initial contact of one foot to corresponding successive initial contact of contralateral foot	Seconds
Single support time	Time period when only one foot is in contact with the ground	Seconds
Double support time	Initial and final periods of the stance phase when two feet are simultaneously in contact with the ground; considered here as a global time	Seconds
Temporophasic parameters		
Stance percentage	Duration of the stance phase relative to the GC time	%GC duration
Single support percentage	Duration of single support relative to the GC time	%GC duration
Double support percentage	Duration of double support (including both in initial and terminal double support) relative to the GC time	%GC duration
Temporospatial parameters		
Gait speed	Speed covered by the entire body in a given time; a product of step length and cadence	m/s (or cm/s where indicated)
Normalised gait speed	Dimensionless normalisation of gait speed to leg length: $speed \times \frac{1}{g \times l_0}$	Dimensionless

4.13. Statistical analysis

Statistical analysis was performed using the IBM Statistical Package for Social Sciences (SPSS Statistics) for Macintosh, Version 25.0 (International Business Machines Corporation, Armonk, NY) and MS Excel V16.12. The distribution of each variable was tested for normality using histograms and the Shapiro-Wilk test, and homogeneity of variances (for ANOVA) were

verified using Levene's test. Data were averaged for left and right limbs[227,359] as the N-poses were symmetrical and no significant differences were apparent between left and right joint angles. Statistical significance was set at an alpha-level of $p < 0.05$. An MCID of > 5°[318] was considered for kinematic angles, while TSPs were interpreted in terms of percentage differences.

Descriptive statistics were mean and standard deviation (SD) for normally distributed data, median and interquartile range (IQR) for non-normal data and percentages for frequencies. Kinematic and TSP outcomes were averaged for each participant across trials, and then averaged across participants. For Study Two, the two participant groups' self-selected gait speeds were compared for a statistically significant difference between PLHIV and SNP using an independent t-test (two-tailed, significance level α = 0.05).

4.13.1. Study One

For the first study, six repeated N-poses and six walking strides (one valid mid-walk stride from each of the recalibrated trials) were analysed per participant. For each participant, six valid strides were used for analysis, resulting in 96 strides for analysis, alongside six calibration repetitions.

4.13.1.1. Concurrent validity (gait data)

Concurrent validity of the gait data was assessed by comparing kinematic waveforms in terms of offset and waveform dissimilarity among the joint angles time histories for raw, calibration-adjusted and calibration-and-time-adjusted myoMOTION output versus VICON-PiG.

Offset error was evaluated using the root-mean-square error (RMSE). The average RMSE value between joint kinematic curves estimated by the myoMOTION and VICON-PiG was computed over the gait cycle and averaged across trials and participants. The RMSE was calculated, for each joint/segment angle, by taking the square root of the mean squared differences between the myoMOTION and VICON-PiG data sets at each timeframe:

$$RMSE = \sqrt{\frac{1}{T}\sum_{t=1}^{T}(x_1 - y_1)^2}$$

where x_t and y_t are the angular values (in degrees) of the myoMOTION and VICON at time frame t, respectively, and T is the number of time points across the gait cycle (i.e. 101 time points due to being normalised to every 1% of the gait cycle).

To determine agreement between myoMOTION and VICON-measured kinematics for walking gait trials, Bland-Altman analyses were conducted for each gait outcome. This method is based on interpretation of residual-like plots and simple calculations.[360] The mean difference (d) between measurements of the same outcome by the two systems (indicating the estimated bias and thus the systematic difference between the systems) and its SD (SD_d) were used to estimate the 95% limits of agreement (LoA):

$$[d] \pm 1{,}96SD_d$$

It is expected that 95% of the differences between the reference and index systems for any participant will fall within these limits. The mean differences between myoMOTION and VICON measurements were plotted against the mean of the values measured by the two systems. Plots were assessed for the extent of the difference between systems and the distribution around the 0 line. The 95% LoA as displayed on the plots were used for visual estimation of how well the two systems agreed. A smaller range between the upper and lower LoA and a closer spread of the estimates around the zero line indicates better agreement between systems.[360] There are no statistical guidelines for a cut-off where the estimated bias and LoA are considered acceptable; this cut-off is based on clinical knowledge and depends on the outcome of interest. Therefore, the MCID of 5° was accepted as a cut-point[318] for angular data.

The effect of a bias error due to the different modelling and calibration processes between systems was evaluated by repeating the statistics mentioned above (RMSE and Bland Altman) using model-corrected (see Section 4.12.1) data.

4.13.1.2. Reliability and repeatability (gait data and N-pose data)

Absolute intra-rater repeatability for setting up the N-pose and absolute myoMOTION within-session reliability during gait was quantified using the standard error of measurement (SEM). For each outcome, a two-way repeated-measure analysis of variance (ANOVA) was performed using data from the six repeat measurements from each of the 16 participants. The SEM was calculated as the square root of the mean-square-error (MS_E) from the ANOVA.[361–363]

$$\mathrm{SEM} = \sqrt{\mathrm{MS_E}}$$

This approach is robust to between-participant variability and thus preferable to calculations based on the intraclass correlation (which is commonly used for SEM calculation).[361,362] By accounting for within-participant variability, the SEM provides an indication of how precisely a test measures a participant's true score.[361,362] The upper 95% confidence limit (CL) of the SEM was calculated by multiplying the SEM by a multiplying factor (i.e. 1.2) which is an SEM-specific parameter based on the number of participants and trials[362]:

$$CL_{SEM}^{95\%} = \sqrt{\frac{dfe}{\chi^2(1-\alpha, dfe)}} \times SEM$$

where the degrees of freedom are given by:

$$dfe = n_p(n_m - 1)$$

where $n_p$is the number of participants and n_m is the number of trials per participant. For the upper 95% CL, 1-α equals 0.05.[328] The upper 95% CL indicates the certainty of the estimated SEM by specifying the highest value that it might have.

The SEM is preferable to other indices (including the intraclass correlation coefficient [ICC]) because the SEM gives a direct indication of measurement uncertainty in degrees, and is thus clinically meaningful.[318] For each trial, parameters were extracted from one mid-walk stride – resulting in six repeated IMC measures of each angle/segment, which were averaged per participant and used for the analysis. Reliable angular results were identified as results that do not differ significantly in clinical terms (i.e. differed by 5° or less) between trials within the session.

4.13.1.3. Accuracy (N-pose data)

The accuracy of a trained rater's ability to set up neutral joint angles and segments for the six N-poses was assessed by comparing, for each joint/segment, the angles obtained from the data provided by the VICON, averaging the six N-pose calibrations, and true anatomical zero (representing the zero-degree angles assumed by the myoMOTION during calibration). To this purpose, the absolute value of the differences (mean absolute difference [MAD]) was calculated and the relevant descriptive statistics (mean and SD) determined. This was done using the data collected during the upright N-pose. Using absolute measures such as RMSE, mean absolute difference and absolute percentage error implies a stricter evaluation since

relative measures may introduce a degree of compensation (having both positive and negative values).[364]

4.13.2. Study Two

For the second study, all analyses were performed separately in PLHIV and SNP, because potential (albeit subtle) differences in consistency and reliability between methods were hypothesised between groups *a priory*. Stride length, step length and gait speed were normalised to participants' leg lengths to enhance comparability (as explained in Section 4.12.5 and Table 4.6). For each participant, six valid strides were used for analysis, resulting in 48 strides for analysis per study group.

4.13.2.1. Concurrent validity

As for Study One, the concurrent validity of myoMOTION gait kinematic angular data (comparison with and without angular offset correction), and additionally for TSPs, was evaluated using RMSE and Bland Altman analyses. Comparative analyses between systems were assessed for SNP and PLHIV separately to evaluate whether gait patterns in a clinical sample with potential gait deviations would affect the system's validity. Additionally, considering the different measurement units between the various TSPs, absolute percentage error (%D) was calculated for these outcomes:

$$\%D = \left|\frac{D_{MR,PiG}}{X_{PiC}}\right|$$

where $D_{MR,PiG}$ is the difference between the parameter values as measured by myoMOTION and VICON-PiG, divided by the parameter value X_{PiG} as measured by VICON-PiG.

In order to interpret percentage error outcomes (including the % SEM – see Section below), a classification criterion of acceptability was used,[364] based on standard statistical thresholds for significance analysis (namely values of 5%, 10%, and 20%).[365] Also, a reference threshold of 5% has been proposed for accuracy error in step length and distance.[366] Four categories were considered: (i) a percentage error of <5% was considered excellent, (ii) between 5% and 10% as good, and (iii) between 10% and less than 20% as sufficient. Values of (iv) 20% or higher were deemed unacceptable.[364]

4.13.2.2. Reliability

Absolute myoMOTION within-session reliability during gait was quantified using the standard error of measurement (SEM), as in Study One. Reliable angular results were again identified as results that do not differ significantly in clinical terms between trials (within-session). In addition, considering that the SEM is presented in terms of the units of measurement of the relevant outcome, for TSPs, the absolute percentage SEM (% SEM) was calculated to enable comparison between the various parameters[367,368]:

$$\%SEM = \left|\left(\frac{SEM}{\bar{X}}\right)\right| \times 100$$

where $\bar{X}$ is the arithmetic mean of the correspondent parameter across the repeated sessions.

PART II

CHAPTER 5

RESULTS: STUDY ONE

5.1. Participant characteristics

Sixteen conveniently selected healthy, able-bodied adults participated in the first validity and reliability study. The full set of kinematic data of all participants could be analysed for both systems (myoMOTION and VICON) as there were no invalid trials or gait cycles and/or technical failures.

Table 5.1 presents the age, gender and anthropometric data of each participant. The predominantly female sample, consisting of fifteen women and one man, had a mean ± standard deviation (SD) age of 20.88 ± 2.39 years. Participants' mean ± SD stature was 1.64 ± 0.08 metres; mean ± SD body mass index (BMI) was 21.68 ± 1.55 kg/m^2 and all participants had a medically confirmed HIV seronegative status.

Table 5.1. Participant characteristics (Study One).

Study code	Age (years)	Gender	HIV status	Height (m)	Weight (kg)	BMI
HIVP1-03[a]	20	Female	Seronegative	1.58	56.40	22.59
HIVP1-04	20	Female	Seronegative	1.63	57.10	21.49
HIVP1-05	22	Female	Seronegative	1.66	60.10	21.81
HIVP1-06	18	Female	Seronegative	1.69	56.40	19.75
HIVP1-07	19	Female	Seronegative	1.72	54.60	18.46
HIVP1-08	20	Male	Seronegative	1.77	64.90	20.72
HIVP1-09	20	Female	Seronegative	1.64	59.40	22.09
HIVP1-10	20	Female	Seronegative	1.63	61.20	23.18
HIVP1-11	21	Female	Seronegative	1.62	51.40	19.71
HIVP1-12	20	Female	Seronegative	1.75	70.60	23.05
HIVP1-13	22	Female	Seronegative	1.70	57.60	19.93
HIVP1-14	21	Female	Seronegative	1.68	65.90	23.35
HIVP1-15	21	Female	Seronegative	1.45	45.80	21.78
HIVP1-16	21	Female	Seronegative	1.56	53.90	22.15
HIVP1-17	20	Female	Seronegative	1.65	63.30	23.25
HIVP1-18	29	Female	Seronegative	1.56	57.00	23.57

Abbreviations: BMI = body mass index; HIV = human immunodeficiency virus; kg = kilograms; m = metres.

[a]The first two participants (coded as HIVP1-01 and 02, respectively) were volunteers who were recruited separately and participated in two separate initial pilot studies (one as a shared pilot study along with another project) with the sole purpose of determining study pragmatics and technical requirements – the data of these two pilot participants were not included in the analysed dataset and therefore the first participant listed is HIVP1-03.

5.2. MyoMOTION validity (gait)

For direct (unadjusted model) comparisons of the systems/models, only pelvic rotation and obliquity root-mean-square errors ($RMSE_{direct}$) were below 5° (Table 5.2). Pelvic tilt and hip flexion/extension (sagittal plane motion) demonstrated the highest $RMSE_{direct}$ and pelvic rotation the lowest. Direct-comparison Bland-Altman analyses revealed biases of ≤ 4.2°, except for sagittal plane pelvic, hip and ankle angles (> 5°). Direct-comparison LoA (LoA_{direct}) were below 5° for all secondary angles (except hip rotation); while all sagittal plane LoA_{direct} exceeded 5°. Figures 5.1 to 5.3 show the Bland Altman plots for the agreement analyses. Figure 5.4 shows the unadjusted kinematic waveform comparison over one gait cycle for a representative participant, graphically demonstrating shape correlations despite model offsets (i.e. direct comparison between system/models).

Calibration-offset corrected (model adjusted) myoMOTION output demonstrated a statistically significant reduction in RMSE for hip flexion/extension: $RMSE_{corrected}$ for all angles were below 5°; except hip rotation. Further time-offset corrections did not produce significant $RMSE_{corrected}$ changes, except for knee flexion/extension (a statistically, but not clinically, significant difference of 1.6°, $p < 0.001$). Calibration-and-time-offset corrections resulted in a maximum bias of 4.7° for pelvic tilt; all other biases were ≤ 1.6°. All calibration-and-time-offset corrected LoA ($LoA_{cal+time}$) were < 5°, except for pelvic tilt which demonstrated an upper limit of 11.8° (Table 5.2).

5.3. MyoMOTION reliability (gait)

Standard error of measurement (SEM) values ranged from 1.1° to 3.8° and were generally below 2°, except for knee flexion/extension, hip rotation and pelvic rotation (Table 5.2).

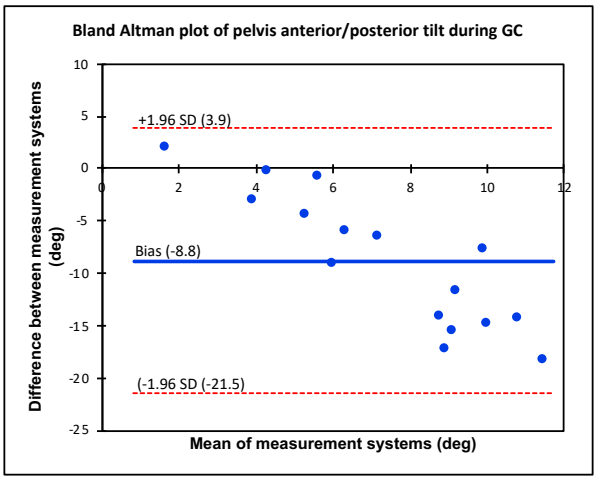
Table 5.2. Concurrent validity and within-session reliability of myoMOTION-measured kinematic gait angles. Concurrent validity was assessed using direct myoMOTION model (MR3) output, as well as modelling- and time-offset corrected outputs.

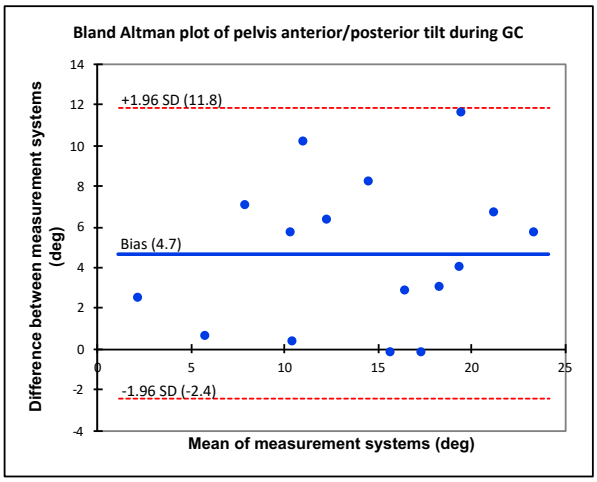
Anatomical angle	Validity: offset (degrees)			Validity: agreement (degrees)		myoMOTION reliability (degrees)
	$RMSE_{direct}$	$RMSE_{cal}$	$RMSE_{cal+time}$	Bias $(LoA)_{direct}$	Bias $(LoA)_{cal+time}$	SEM (upper 95%CL)
Pelvis A/P Tilt	14.8°± 5.4°	2.2° ± 2.1°*	2.2°±1.2°	-8.8° (-21.5° to 3.9°)	4.7° (-2.4° to 11.8°)	1.1° (1.3°)
Pelvis Obl	4.2°±1.3°	4.3°±1.4°	4.6°±1.5°	-0.0° (-0.3° to 0.2°)	0.0° (-0.1° to 0.1°)	1.2° (1.4°)
Pelvis Rot	2.9°±1.0°	3.8° ± 1.8°*	3.7° ± 1.8°	0.1° (-0.5° to 0.7°)	0.1° (-0.4° to 0.5°)	3.8° (4.6°)
Hip F/E	9.6°±5.8°	3.8° ± 1.4°*	3.6° ± 1.2°	-7.8° (-22.6° to 7.1°)	-0.9° (-4.8° to 3.1°)	1.8° (2.2°)
Hip Ab/Ad	5.0°±1.9°	3.2° ± 1.2°*	3.6° ± 1.3°	3.5° (0.2° to 6.9°)	-0.8° (-2.6° to 0.9°)	1.4° (1.7°)
Hip Rot	8.1°±3.7°	6.0° ± 2.2°*	6.1°± 2.2°	-4.2° (-13.7° to 5.3°)	-1.2° (-4.6° to 2.2°)	3.4° (4.1°)
Knee F/E	7.1°±4.0°	4.9°± 2.1°*	3.3°±1.2°*	2.8° (-8.0° to 13.8°)	1.6° (-1.4° to 4.5°)	2.4° (2.9°)
Ankle DF/PF	7.1°±2.8°	3.7° ± 1.4°*	3.0° ± 1.1°	-6.0° (-12.0° to -0.1°)	0.1° (-2.5° to 2.6°)	1.9° (2.3°)

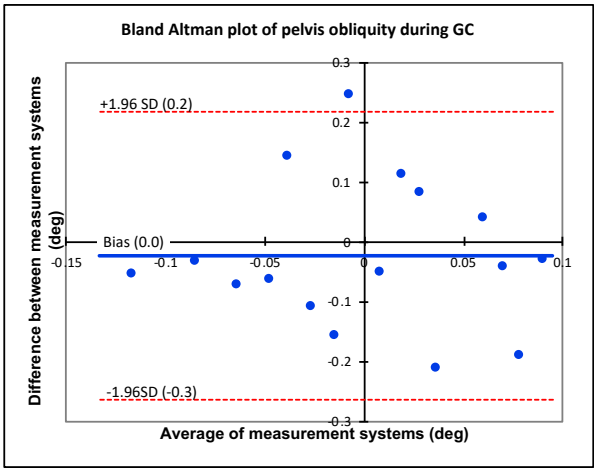
Abbreviations: 95%CL = 95% Confidence Limits of the standard error of measurement; A/P = anterior/posterior; Ab/Ad = abduction/adduction; cal = model adjusted for calibration; cal+time = model adjusted for calibration and time; DF/PF = dorsiflexion/plantarflexion; direct = direct comparison of model output; F/E = flexion/extension; LoA = limits of agreement; Obl = obliquity; RMSE = root-mean-square-difference; Rot = rotation; SEM = standard error of measurement.
RMSE presented as mean ± standard deviation.
** indicates a statistically significant difference between direct and cal-adjusted, or between cal-adjusted and cal+time-adjusted RMSE ($p < 0.05$, paired t-test).*
Bold print indicates clinically significant joint angle values (> 5°)

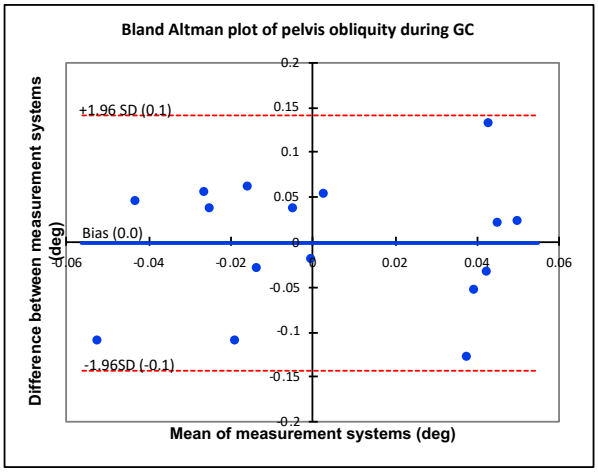
Unadjusted myoMOTION model

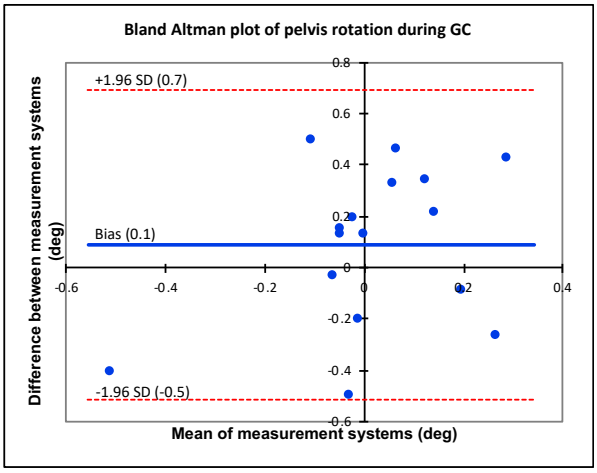
Adjusted myoMOTION model











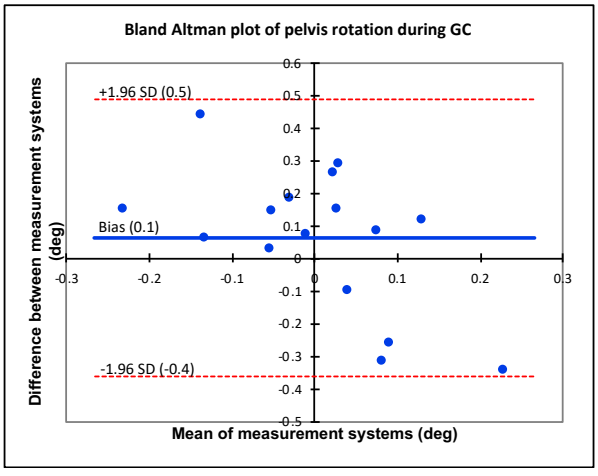


Figure 5.1. Bland Altman plots for pelvis tilt, obliquity and rotation, showing bias (blue solid line) and Limits of Agreement (red dashed lines) between the myoMOTION and VICON systems in Study One. The left column shows the unadjusted results, and the right column the model-corrected results.

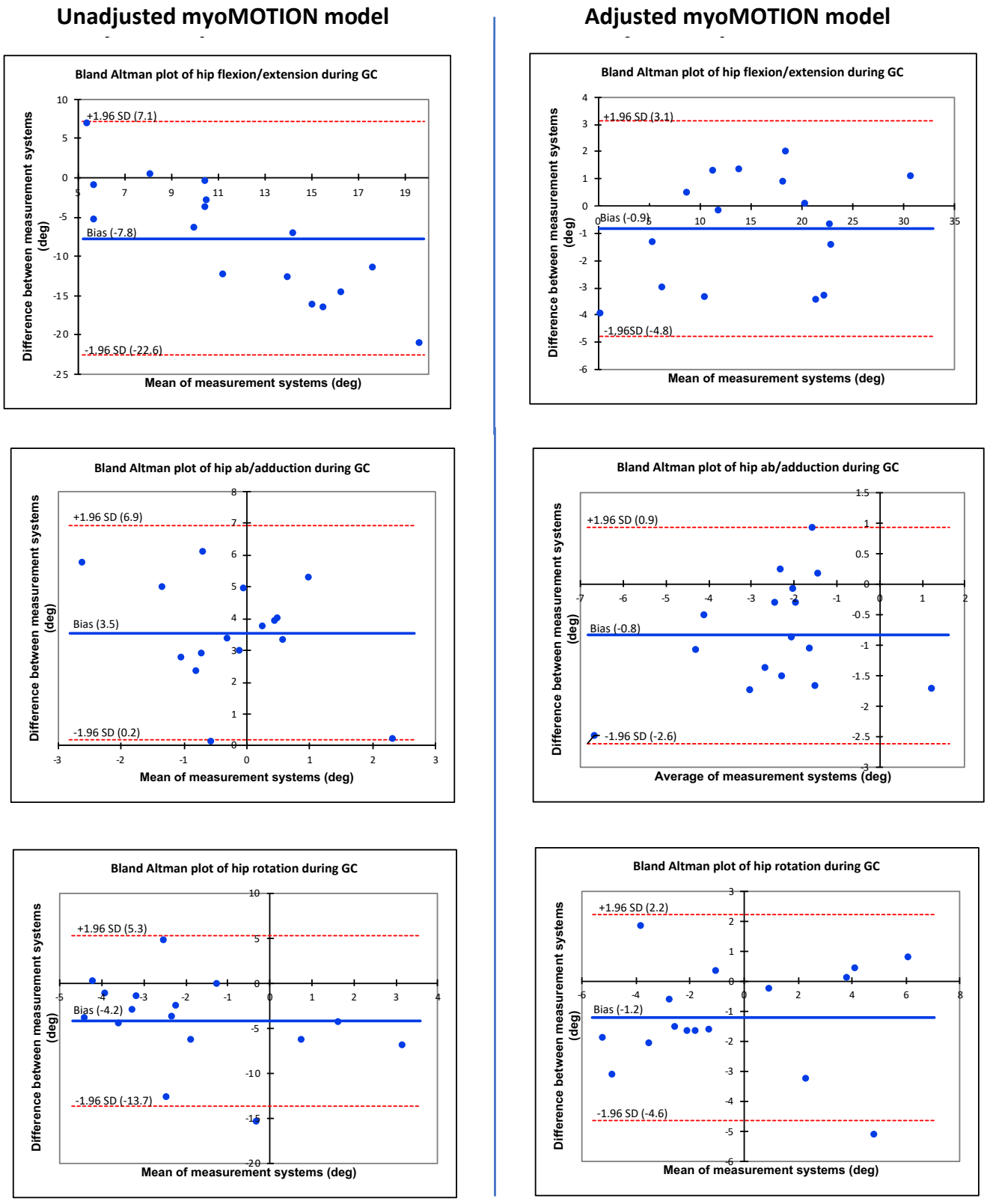


Figure 5.2. Bland Altman plots for hip flexion/extension, ab/adduction and rotation, showing bias (blue solid line) and Limits of Agreement (red dashed lines) between the myoMOTION and VICON systems in Study One. The left column shows the unadjusted results, and the right column the model-corrected results.

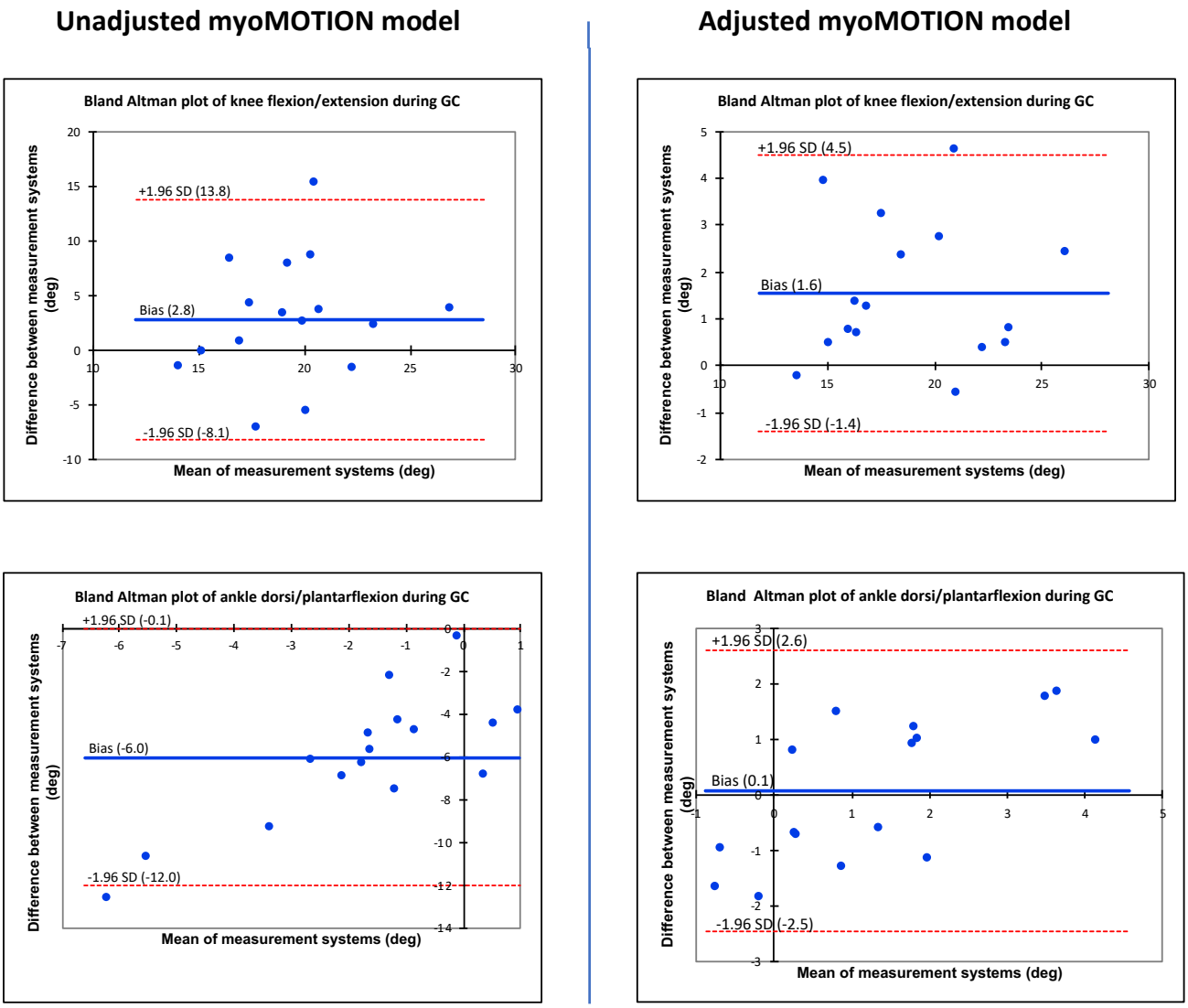


Figure 5.3. Bland Altman plots for knee flexion/extension and ankle dorsi/plantarflexion, showing bias (blue solid line) and Limits of Agreement (red dashed lines) between the myoMOTION and VICON systems in Study One. The left column shows the unadjusted results, and the right column the model-corrected results.

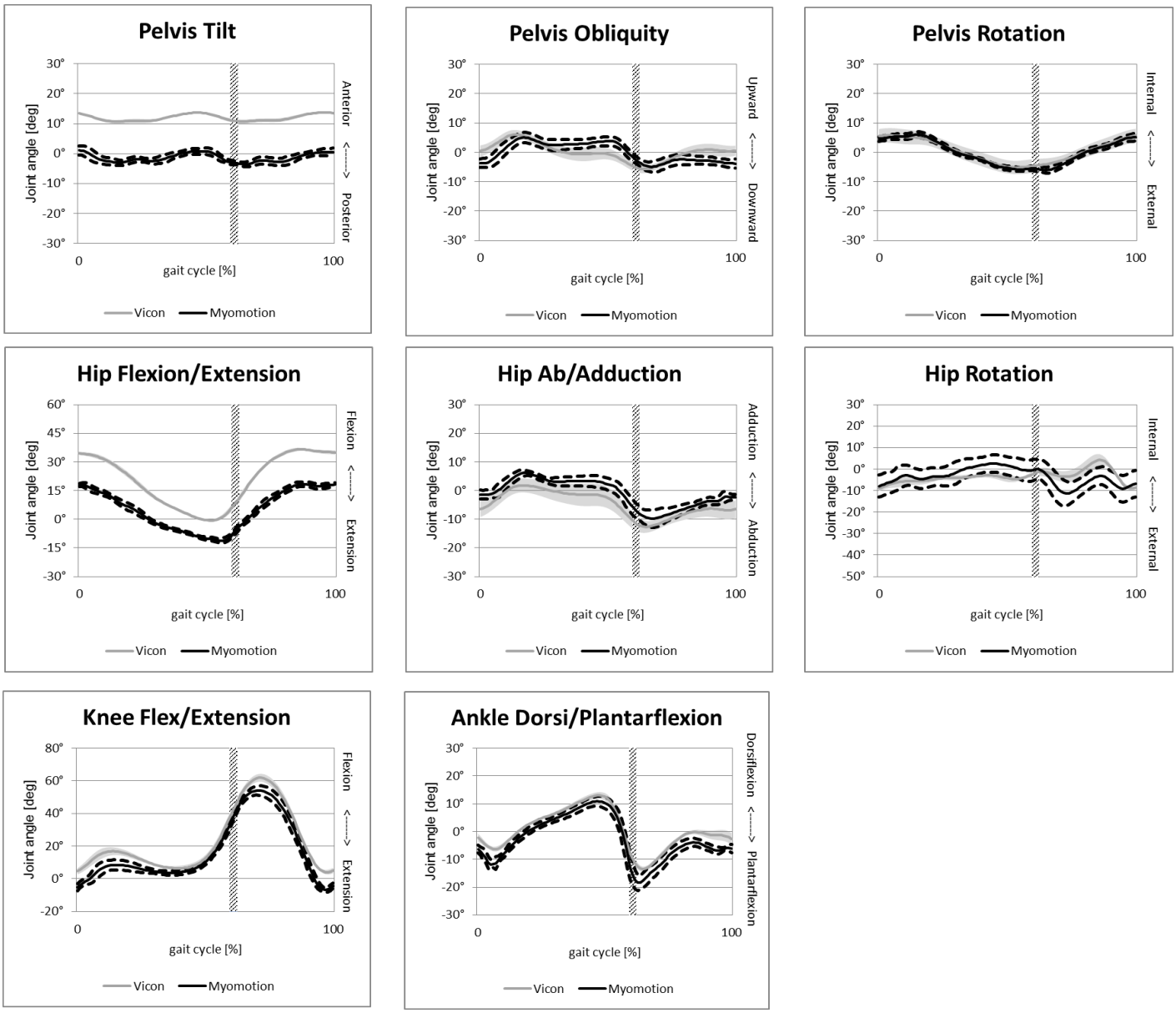


Figure 5.4. Comparative gait traces produced by the (unadjusted) myoMOTION model (black) and VICON-PiG (grey) for a representative participant. Solid lines represent the mean angles over one gait cycle. The dashed lines represent the standard deviation (SD) of the myoMOTION, and the grey shaded areas the SD of the VICON mean. Systematic angular offsets between mean values produced by the different systems/models are most apparent for pelvis tilt and hip flexion/extension.

5.4. N-pose accuracy

Mean absolute difference (MAD) values were below 5° for all coronal angles and transverse ankle, hip and pelvic angles (Table 5.3). Although knee flexion demonstrated a low MAD (1.1°), its SD indicated clinically significant random error, and visual inspection revealed a

single outlier (13.9°). MAD exceeded 5° for ankle dorsiflexion and knee rotation; SDs (< 5°) confirming systematic offset. The hip and pelvis both demonstrated clinically significant sagittal MAD with high SDs. These angular means demonstrated large ranges with no clear outliers. Foot and pelvic errors demonstrated small MAD values.

5.5. N-pose repeatability

All SEM values were below 2.2°; the highest value being observed for knee rotation and the best repeatability (lowest SEM) for ankle inversion (0.3°). Knee rotation showed the highest upper 95% confidence limit (CL), namely 2.6° (Table 5.3).

Table 5.3. Accuracy and repeatability for six repeated N-pose implementations.

Anatomic angle	Accuracy (degrees)		Repeatability (degrees)	
	MAD		SEM	
	Mean	SD	Mean	Upper 95% Confidence Limit
Ankle dorsiflexion	**6.1°**	2.5°	1.1°	1.3°
Ankle inversion	0.2°	1.2°	0.3°	0.4°
Ankle rotation	3.8°	4.7°	1.0°	1.2°
Hip flexion	**6.9°**	**8.3°**	1.7°	2.0°
Hip adduction	4.4°	2.3°	0.9°	1.1°
Hip rotation	2.9°	4.8°	1.6°	1.9°
Knee extension	1.1°	**5.3°**	1.9°	2.3°
Knee varus	3.5°	2.6°	0.4°	0.5°
Knee rotation	**6.5°**	4.6°	2.2°	2.6°
Pelvic anterior tilt	**13.4°**	**6.3°**	1.2°	1.4°
Pelvic obliquity	0.0°	1.1°	0.7°	0.8°
Pelvic rotation	0.5°	3.0°	1.5°	1.8°
Foot progression	1.8°	1.9°	1.4°	1.7°

Abbreviations: MAD = mean absolute difference; n = number of participants; SEM = standard error of measurement.
MAD values are presented as the mean ± standard deviation.
Bold values indicate results of clinical significance (>5°).

5.6. Chapter summary

This chapter presented the results of Study One regarding the validity and reliability testing conducted using the myoMOTION system for analysing standard kinematic gait analysis outcomes, using a convenience sample of university volunteers. Findings demonstrated that frequently recalibrated myoMOTION measurements provide reliable lower limb gait kinematics in healthy adults and highly compare to VICON-PiG output after accounting for inherent biomechanical modelling differences. N-pose calibrations can be implemented/instructed accurately (for most outcomes) and consistently using standardised instructions. The repeated N-pose setups in-between gait trials did not adversely affect the reliability of the gait outcomes. Because of an inherent modelling offset existing between systems, low concurrent validity (>5° difference) was observed for some direct model comparisons (i.e. sagittal plane ankle, hip, knee and pelvis angles, and transverse plane hip angles). However, good agreement was consistently observed once the modelling differences were accounted for. Chapter 6 describes the results from the next phase of testing, involving additional and clinically relevant gait outcomes (particularly in terms of describing elderly gait) assessed in a community-specific sample including PLHIV and SNP.

PART II

CHAPTER 6
RESULTS: STUDY TWO

6.1. Participant characteristics

A total of sixteen adults (eight people living with HIV-1 infection [PLHIV] and eight seronegative participants [SNP]) participated in the second laboratory-based validity and reliability study. The full set of kinematic data as required for the study (i.e. six gait cycles per participants) of all participants was analysed for both systems (myoMOTION and VICON).

Characteristics of the participants in the PLHIV and SNP groups are presented in Table 6.1; including HIV-specific characteristics for PLHIV. Overall the sample was predominantly female (75% of SNP and 50% of PLHIV). Both groups entirely comprised of participants self-identified as coloured. PLHIV were on average 8.56 years older and 7.71 kg heavier than SNP; while the groups were similar regarding leg length, height and BMI. Mean gait speed as measured by VICON tended to be slower in PLHIV than in SNP (1.17 ± 0.14 m/s in PLHIV versus 1.30 ± 0.11 m/s in SNP) – this difference was not statistically significant (p = 0.057) but may be considered clinically significant[369] (mean difference 0.13 m/s).

6.1.1. HIV-related characteristics

The median (Q1 – Q3) CD4+ cell count amongst PLHIV was 505 (449 – 651) cells/µL, and only two (25%) PLHIV had an undetectable viral load (HIV-1 RNA <50 cp/mL). Half of PLHIV had an HIV-duration of less than two years and only one participant (12.5%) had an HIV duration of > 15 years. The majority (n = 6; 75%) of PLHIV were using HAART, all of which were NRTI/NNRTI-based first line regimes, with a median duration of 71.5 weeks (range: 16 to 465 weeks) or 1.38 years.

Table 6.1. Demographic, anthropometric and HIV-specific sample characteristics.

Characteristic	SNP (n = 8)	PLHIV (n = 8)
Demographic and anthropometric characteristics		
Age in years†	26.24 (23.51 – 31.38)	34.80 (30.73 – 45.14)
Female gender	75%	50%
Ethnicity/race		
Coloured	100%	100%
Height (m)	1.59 ± 0.09	1.64 ± 0.08
Weight (kg)	49.51 ± 11.24	57.22 ± 9.99
BMI (kg/m^2)	19.54 ± 3.03	21.19 ± 3.50
Leg length (cm)	84.74 ± 5.53	85.88 ± 4.41
Gait speed (m/s)[#]	1.30 ± 0.11	1.17 ± 0.14
HIV-specific characteristics (n = 8)		
Most recent CD4+ T-cell count (cells/μL)[#]	--	505 (440 – 651
Percent with detectable HIV-1 RNA (>50 cp/mL)	--	75%
Time since HIV-1 diagnosis:	--	
<2 years	--	50%
2 – 5 years	--	25%
>5<15 years	--	12.5%
>15 years	--	12.5%
Percent on HAART	--	75%
Median HAART duration (weeks)[#]	--	71.5 (16 – 465)
Percent on first line HAART	--	100%
Percent on NRTI/NNRTI	--	100%

†*presented as median (first quartile to third quartile).*
All other values presented as mean ± standard deviation, or percentage.
Abbreviations: HAART = highly active antiretroviral therapy; HIV-1 = human immunodeficiency virus 1; PLHIV = people living with HIV-1 infection; RNA, = ribonucleic acid; SNP = HIV-seronegative participants.

6.2. Concurrent validity of the myoMOTION versus VICON in PLHIV and SNP

6.2.1. Gait TSP parameters

Table 6.2 presents the RMSE, absolute % error, bias and LoA between myoMOTION and VICON measurements for each TSP outcome and separately by HIV-serostatus. In addition, Figures 6.1 to 6.3 graphically present agreement between systems for the TSPs in the form of Bland Altman plots (PLHIV and SNP depicted on a single graph using blue and red colouring respectively).

RMSE, bias and LoA between systems were close to zero for all temporal parameters as well as gait speed (especially once normalised for leg length), as well as for the spatial parameters that were normalised to leg length. This was the case for PLHIV as well as SNP. For spatial parameters, RMSE, bias and LoA values in PLHIV were within 1.2 cm or less of those observed in SNP.

In both groups, the myoMOTION tended to underestimate absolute step and stride length compared to the reference, although the absolute percentage error was small: 1.66% and 2.51% respectively for step and stride length in SNP and 1.07% and 2.28% for step and stride length in PLHIV. For temporal parameters, RMSE values, biases and % errors were close to identical in the two groups.

Across all parameter outcomes, percentage differences were generally below 3%, except for double support time (both absolute and expressed as a percentage of the gait cycle). In both groups, these parameters had the largest discrepancies in percentage error. The actual double support duration had a small offset error (RMSE 0.03s in both groups) and good agreement (bias 0.01s in both groups, with similar and small LoA in both groups) but due to the short duration of each stride, when normalised to a percentage of the gait cycle, the double support percentage showed less agreement. The largest difference in measurement was a 7.4% error in double support duration in SNP (also the highest percentage error for PLHIV, namely 5.79%), which, for both groups, equates to a 0.012s or 12ms time difference. The RMSE and bias associated with this outcome was however very small, as were the LoA – which suggested that the highest systematic error likely to be observed between systems in 95% of individuals is a 0.07s difference

Table 6.2. Concurrent validity of myoMOTION-measured TSPs (direct output). Analyses were performed separately in people living with HIV-1 (PLHIV) and seronegative participants (SNP).

Gait parameter	SNP				PLHIV			
	Offset		Agreement		Offset		Agreement	
	RMSE (mean ±SD)	%D	Bias	95% LoA	RMSE (mean ±SD)	%D	Bias	95% LoA
Spatial parameters								
Step length (cm)	3.22 ± 1.63	1.66%	-1.05	-5.83; 3.72	4.38 ± 2.01	1.07%	-0.74	-4.95; 3.47
Normalised step length	0.04 ± 0.02	1.66%	-0.01	-0.07; 0.04	0.05 ± 0.02	1.07%	-0.01	-0.05; 0.04
Stride length (cm)	4.46 ± 3.51	2.51%	-3.26	-11.45; 4.92	4.46 ± 2.62	2.28%	-2.95	-10.68; 4.78
Normalised stride length	0.05 ± 0.04	2.51%	-0.04	-0.13; 0.05	0.05 ± 0.03	2.28%	-0.03	-0.11; 0.05
Temporal parameters								
Stance time (sec)	0.02 ± 0.01	1.22%	0.01	-0.03; 0.04	0.03 ± 0.02	1.06%	0.01	-0.04; 0.05
Step time (sec)	0.03 ± 0.02	0.12%	<0.00	-0.03; 0.03	0.03 ± 0.02	0.17%	<0.00	-0.02; 0.02
Single support time (sec)	0.02 ± 0.01	1.21%	-0.01	-0.03;0.02	0.02 ± 0.01	1.43%	-0.01	-0.02; 0.01
Double support time (sec)	0.03 ± 0.01	7.40%	0.01	-0.04; 0.06	0.03 ± 0.03	5.79%	0.01	-0.05; 0.07
Temporophasic parameters								
Stance time (%GC)	1.72 ± 0.39	0.98%	0.57	-1.37; 2.51	1.97 ± 1.23	1.13%	0.69	-2.00; 3.43
Single support time (%GC)	2.44 ± 1.35	1.37%	-0.57	-3.53; 2.39	2.31 ± 1.40	1.26%	-0.50	-3.24; 2.24
Double support time (%GC)	3.01 ± 1.14	6.96%	1.14	-3.58; 5.86	2.68 ± 2.29	5.69%	1.18	-4.14; 6.51
Temporospatial parameters								
Gait speed (m/s)	0.04 ± 0.03	2.68%	-0.03	-0.11; 0.04	0.04 ± 0.03	2.13%	-0.03	-0.10; 0.05
Normalised gait speed	0.01 ± 0.01	2.68%	-0.01	-0.04; 0.01	0.01 ± 0.01	2.13%	-0.01	-0.03; 0.02

Abbreviations: %D = percentage difference; cm = centimetres; GC = gait cycle; LoA = limits of agreement; m/s = meters per second; PLHIV = people living with HIV-1 infection; RMSE = root-mean-square error; sec = seconds; SNP = HIV-seronegative participants.

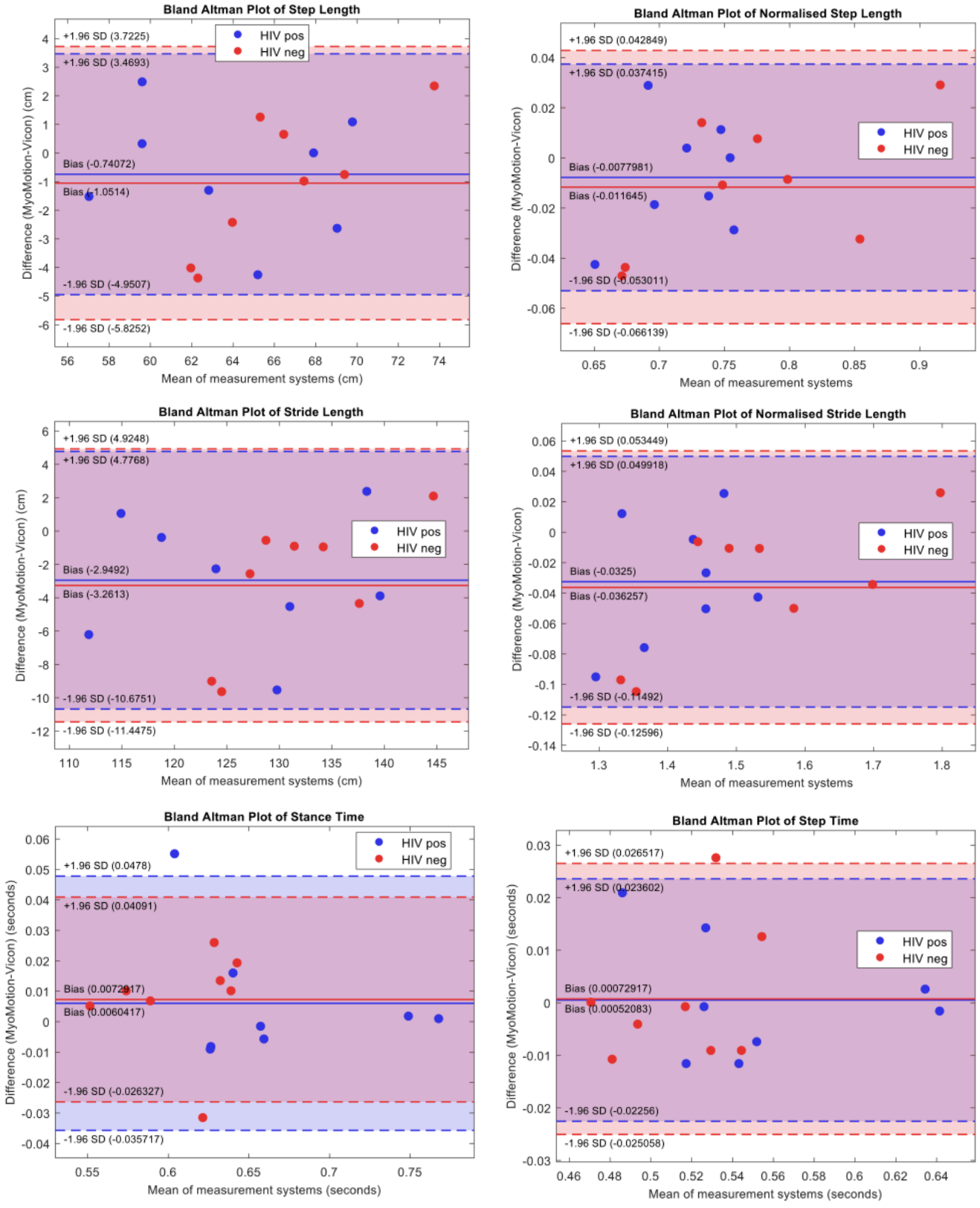


Figure 6.1. Bland Altman plots showing bias (solid lines) and Limits of Agreement (dashed lines) between systems for TSPs in PLHIV and SNP (Study Two). These data are direct myoMOTION output, since modelling differences did not affect TSPs. Blue colouring indicates results for PLHIV and red colouring indicates results for SNP.

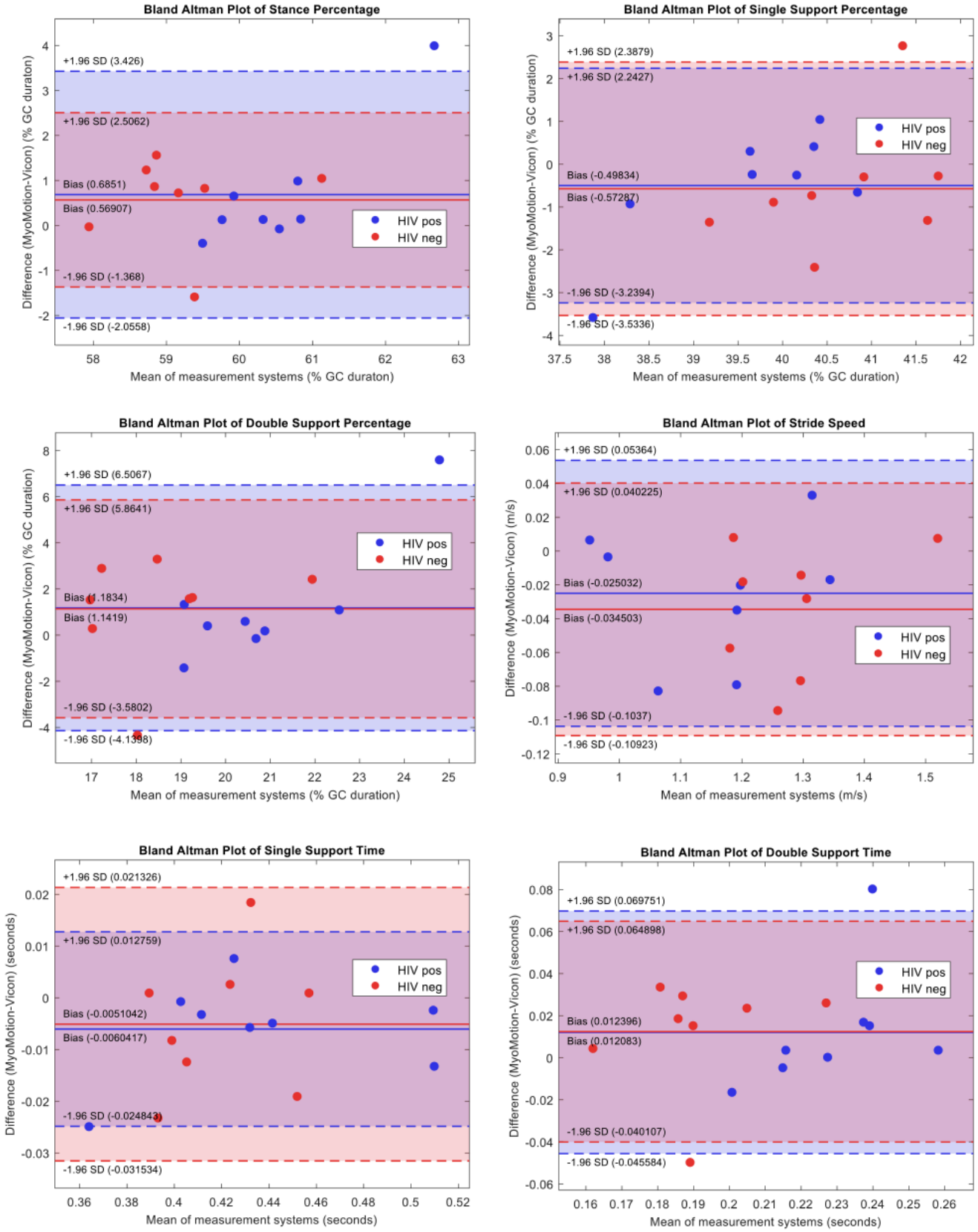


Figure 6.2. Bland Altman plots showing bias (solid lines) and Limits of Agreement (dashed lines) between systems for TSPs in PLHIV and SNP (Study Two). These data are direct myoMOTION output, since modelling differences did not affect TSPs. Blue colouring indicates results for PLHIV and red colouring indicates results for SNP.

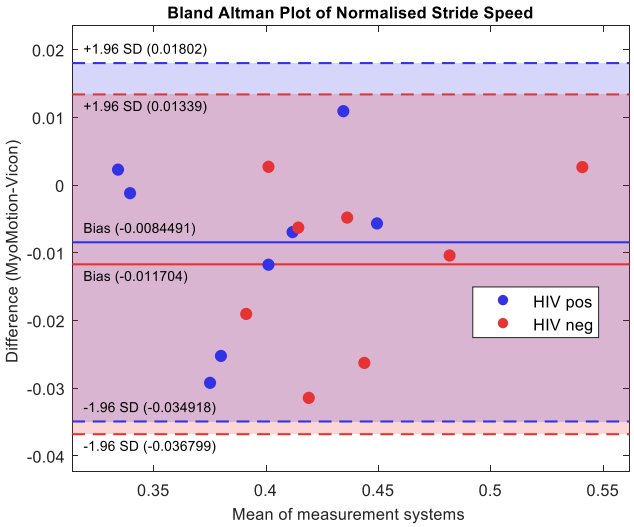


Figure 6.3. Bland Altman plots showing bias (solid lines) and Limits of Agreement (dashed lines) between systems for TSPs (normalised stride speed) in PLHIV and SNP (Study Two). These data are direct myoMOTION output, since modelling differences did not affect TSPs. Blue colouring indicates results for PLHIV and red colouring indicates results for SNP.

6.2.2. Gait kinematics

For kinematic measurements, RMSEs and results from Bland Altman analyses between the myoMOTION and VICON systems are reported in Tables 6.2 (direct output) and 6.3 (calibration-offset adjusted output). Results are presented separately for PLHIV and SNP. Agreement between systems regarding kinematic angles is graphically presented using gait graphs in Figures 6.4 to 6.6. Bland Altman plots are not included in this dissertation due to the large number of outcomes and subsequent space requirements.

6.2.2.1. Direct output comparison

In PLHIV as well as in SNP, good agreement existed between the ranges of motion (ROM) measured by the myoMOTION and VICON systems (visualised in Figure 6.2). Generally, RMSEs, biases and LoA were larger in PLHIV versus SNP (although remaining within 2° from those observed in SNP). Comparing direct myoMOTION output to VICON revealed between-system differences that were more apparent regarding discrete angles (i.e. angular values at specific time points of the gait cycle), and less so in joint/segment ROM (i.e. the motion range [difference] between minimum and maximum angle). Considering ROM, in both groups (PLHIV and SNP), differences between the systems were mostly below 5°; except for hip flexion ROM (during entire gait cycle and during pre-swing to initial swing). Regarding discrete angles, between-system differences exceeded 5° for fewer outcomes measured in SNP;

differences were most likely to exceed 5° for discrete knee flexion/extension angles. As expected, due to the different model definitions and calibration procedures, discrete joint and segment angles in the sagittal plane were mostly underestimated by the myoMOTION relative to VICON (indicated by negative biases).

For the pelvis, RMSEs were smaller than 5° for all ROMs and only exceeded 5° for the two discrete segment angles under investigation (i.e. pelvis rotation angle at initial contact and peak pelvis anterior tilt). The latter demonstrated particularly large LoA in both groups (-24.2° and -24.4° in PLHIV and SNP respectively), also showing the highest RMSE (12.5° ± 5.9° and 10.2° ± 7.1° in PLHIV and SNP respectively) and biases (-12.5° and -10.1°). For both PLHIV and SNP, peak anterior pelvis tilt during the gait cycle showed the largest offsets and poorest agreement between systems, and pelvis tilt ROM during the gait cycle the smallest.

In both groups, trends in between-system differences were similar, hip flexion angle at initial contact, peak hip flexion during swing, and peak hip extension during stance showed the largest RMSEs, biases and LoA; and hip flexion ROM from stance to swing the lowest. However, between-system differences were larger in PLHIV and often exceeded 5° even for ROM measurements, with only hip flexion ROM during LR (sagittal plane), hip abduction ROM during mid-stance and hip adduction ROM during loading response showing RMSEs below 5° in this group.

For knee ROM measurements, between-system differences were below 5° in PLHIV as well as SNP, although some LoA exceeded 5° in both groups. Discrete knee angles showed larger differences and mostly exceeded 5°; except for knee flexion at initial contact in PLHIV. In contrast to observations for ROM measurements, between-system differences in discrete knee angles in the sagittal plane (angles often reported to be sensitive to gait speed differences) were larger in SNP than in PLHIV. Peak knee flexion angle during stance (loading response) showed the largest offsets (RMSE 15.3° ± 7.5° and 11° ± 7.5° in SNP and PLHIV respectively) and poorest agreement (biases of 14.2° and 9.8° in SNP and PLHIV respectively) between systems, with large LoA.

Ankle ROM measurements showed RMSEs, biases and LoA to be smaller than 5° in both groups. Discrete ankle angles also showed differences of below 5° in SNP; in contrast, differences for these discrete outcomes somewhat exceeded 5° in PLHIV. Specifically, in ascending order, peak angle plantarflexion, ankle plantarflexion angle at toe-off and ankle dorsiflexion angle at initial contact showed the largest RMSEs, biases and LoA. This trend was mirrored in SNP, although between-system differences remained below 5° in SNP.

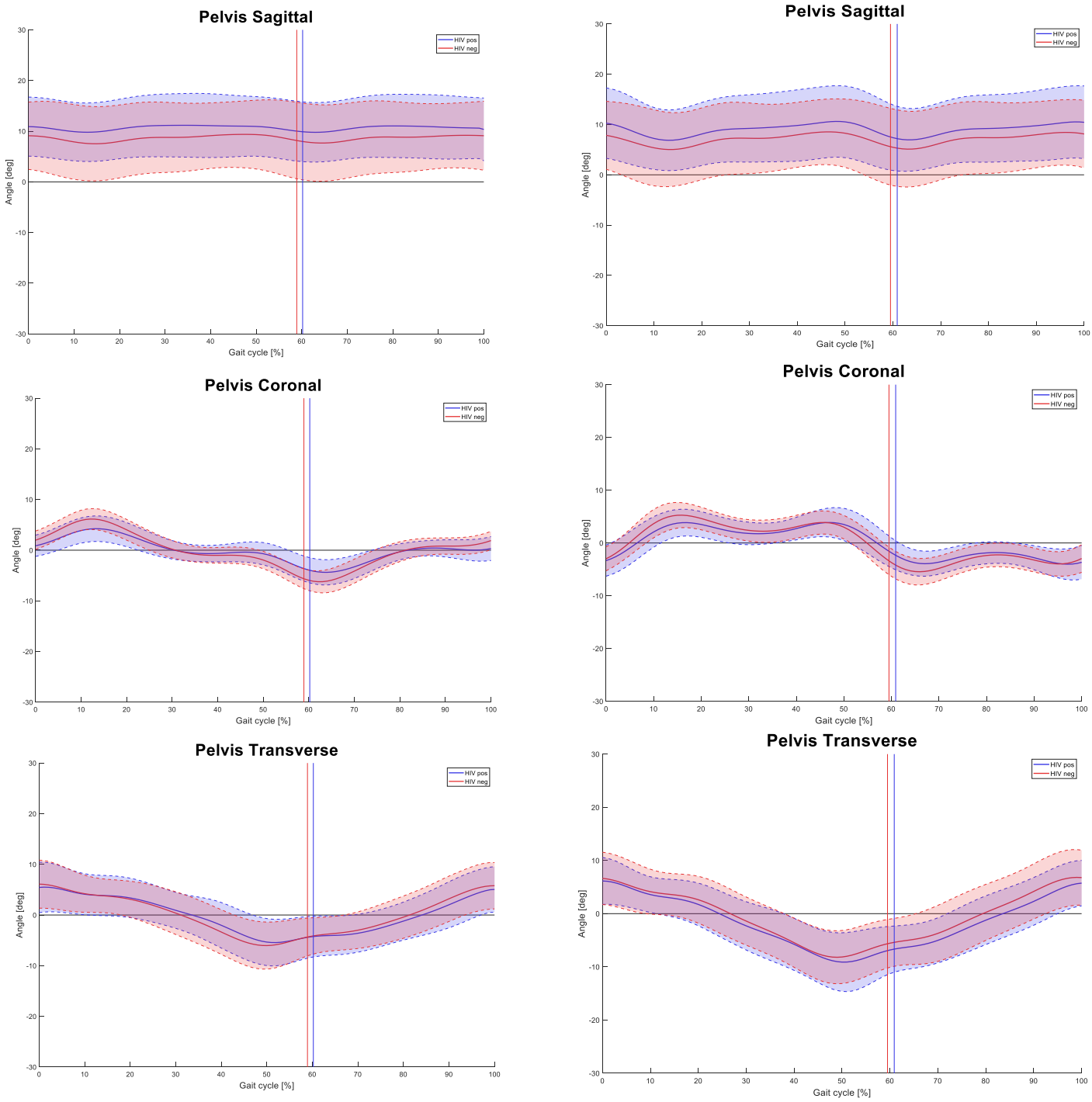


Figure 6.4. Comparative gait traces between PLHIV (blue) and SNP (red), showing pelvis kinematics over one gait cycle as measured by VICON-PiG (left column) and myoMOTION (right column) respectively. The graphs illustrate the mean (solid lines) ± standard deviation (shaded areas bounded by dashed lines) estimated by each system for each group.

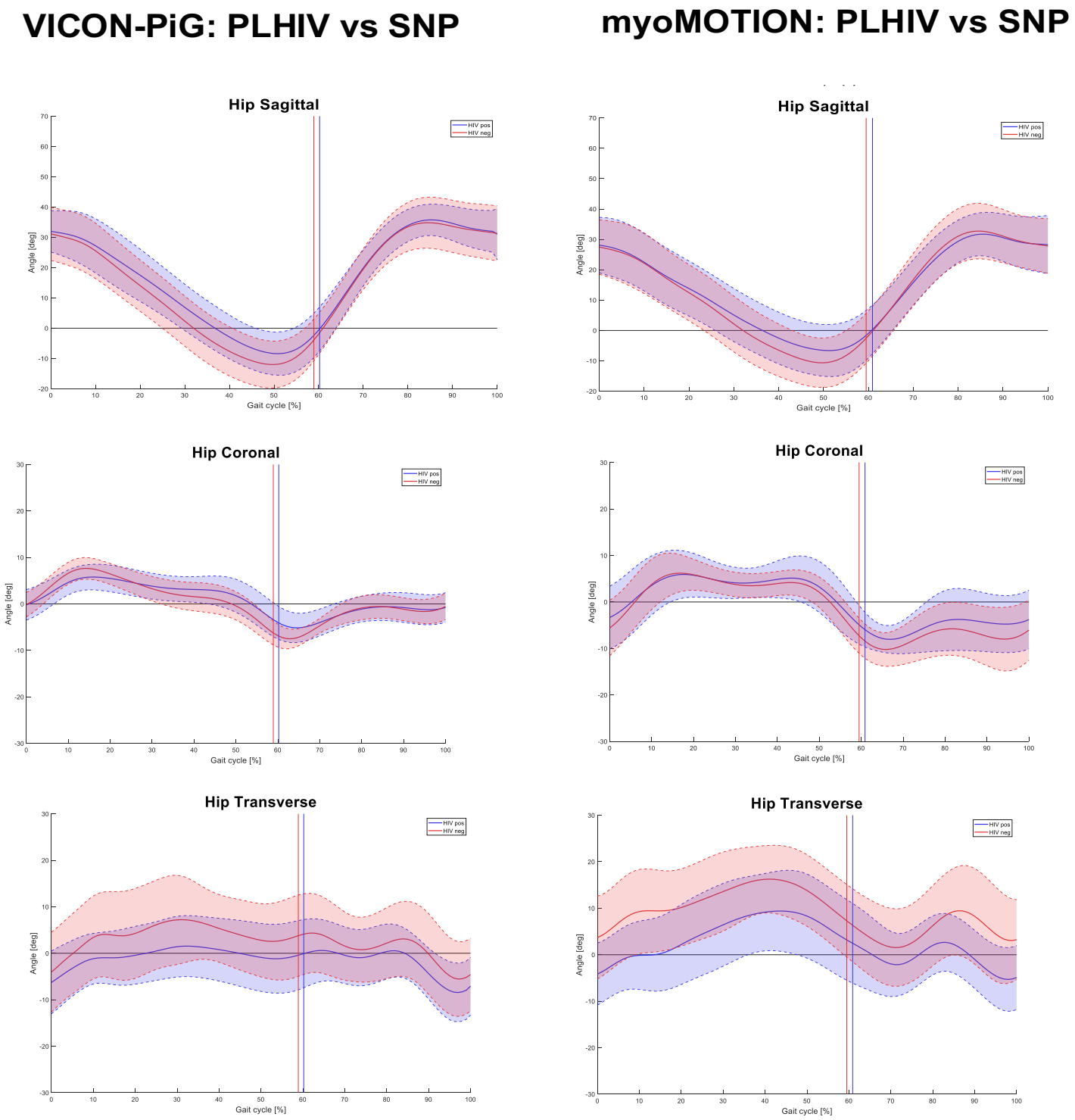


Figure 6.5. Comparative gait traces between PLHIV (blue) and SNP (red), showing hip kinematics over one gait cycle as measured by VICON-PiG (left column) and myoMOTION (right column) respectively. The graphs illustrate the mean (solid lines) ± standard deviation (shaded areas bounded by dashed lines) estimated by each system for each group.

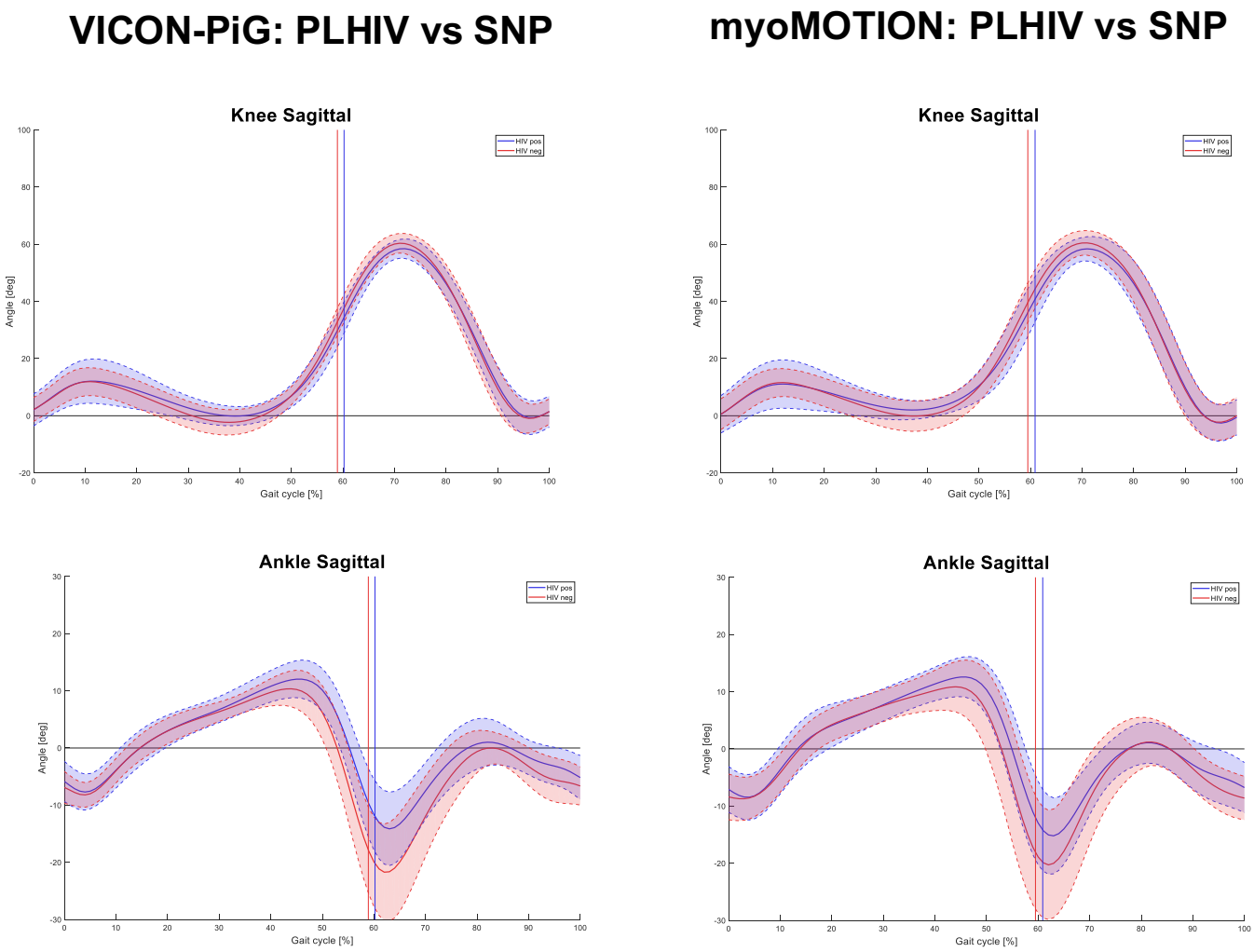


Figure 6.6. Comparative gait traces between PLHIV (blue) and SNP (red), showing sagittal plane knee and ankle kinematics over one gait cycle as measured by VICON-PiG (left column) and myoMOTION (right column) respectively. The graphs illustrate the mean (solid lines) ± standard deviation (shaded areas bounded by dashed lines) estimated by each system for each group

Table 6.3. Concurrent validity of myoMOTION-measured gait kinematics (direct output). Analyses were performed separately in people living with HIV (PLHIV) and seronegative participants (SNP).

Kinematic angle	SNP			PLHIV		
	Offset	Agreement		Offset	Agreement	
	RMSE (mean ± SD)	Bias	95% LoA	RMSE (mean ± SD)	Bias	95% LoA
Pelvis						
Pelvis tilt ROM during GC (°)	2.1 ± 1.1	2.0	-0.1; 4.1	2.9 ± 1.8	2.2	-2.2; 6.5
Peak pelvis anterior tilt during GC (°)	10.2 ± 7.1	-10.1	-24.4; 4.2	12.5 ± 5.9	-12.5	-24.2; -0.8
Pelvis obliquity ROM during GC (°)	2.4 ± 1.7	-0.6	-6.2; 5.0	4.7 ± 3.3	1.7	-9.3; 12.7
Pelvis rotation ROM during GC (°)	3.3 ± 1.7	3.0	-0.6; 6.6	4.1 ± 2.4	3.7	-1.2; 8.6
Pelvis rotation at IC (°)	5.5 ± 2.0	1.2	-1.0; 3.5	5.7 ± 4.5	2.2	-1.0; 5.5
Hip						
Hip flexion ROM during GC (°)	3.5 ± 1.1	-3.1	-6.0; -0.2	5.5 ± 2.1	-5.0	-9.1; -1.0
Hip flexion ROM during LR (°)	1.9 ± 1.5	0.5	-1.3; 2.3	2.3 ± 1.3	1.3	-2.0; 4.6
Hip flexion ROM, PS to IS (H3) (°)	3.1 ± 1.4	<0.0	-5.2; 5.1	5.1 ± 4.4	-1.6	-10.4; 7.2
Hip flexion angle at IC (°)	8.7 ± 5.1	-5.4	-22.0; 11.3	10.6 ± 4.5	-9.4	-22.1; 3.4
Peak hip flexion during swing (°)	7.8 ± 4.8	-3.7	-20.1; 12.7	10.0 ± 4.4	-9.0	-21.0; 3.0
Peak hip extension during stance (°)	7.3 ± 3.9	0.6	-16.0; 17.1	6.7 ± 3.7	4.0	-8.8; 16.7
Hip abduction ROM during mid-stance (°)	3.2 ± 1.7	<0.0	-5.3; 5.4	4.5 ± 3.1	3.3	-3.1; 9.6
Hip adduction ROM during loading response (°)	3.2 ± 1.4	2.8	-0.1; 5.6	2.9 ± 1.9	2.5	-1.4; 6.3
Hip internal rotation ROM during GC (°)	5.2 ± 1.4	1.7	-6.0; 9.5	5.7 ± 3.3	2.7	-6.7; 12.1
Knee						
Knee flexion ROM during GC (°)	2.2 ± 0.9	0.4	-3.1; 3.9	3.0 ± 1.5	1.4	-3.3; 6.0
Knee flexion ROM during stance (K1) (°)	2.8 ± 1.3	1.6	-1.9; 5.1	1.9 ± 1.7	0.7	-2.0; 3.4
Knee flexion ROM from stance to swing (K3) (°)	2.5 ± 1.3	-1.7	-5.1; 1.6	2.6 ± 1.3	-1.5	-5.5; 2.5
Knee extension ROM, MSt to TSt (K2) (°)	2.5 ± 1.3	-2.1	-4.9; 0.7	3.4 ± 1.8	-3.0	-6.7; 0.6

Knee flexion at IC (°)	7.8 ± 1.9	5.8	-2.2; 13.7	4.8 ± 3.3	2.2	-6.3; 10.7
Peak knee flexion during stance, LR (°)	15.3 ± 7.5	14.2	-0.4; 28.8	11.0 ± 7.5	9.8	-5.5; 25.0
Peak knee extension during stance (°)	9.3 ± 2.8	-8.3	-1.1; -15.5	5.3 ± 4.0	-4.0	-12.5; 4.6
Peak knee flexion during swing (°)	8.5 ± 2.5	7.6	1.2; 14.1	5.4 ± 3.6	4.1	-4.1; 12.3
Ankle						
Ankle dorsiflexion ROM during stance (A1) (°)	2.7 ± 1.1	2.0	-1,1; 5.2	2.7 ± 0.7	1.7	-1.5; 4.9
Ankle dorsiflexion ROM during swing (°)	2.3 ± 1.8	1.1	-3.3; 5.4	2.4 ± 1.0	1.1	-2.3; 4.6
Ankle plantarflexion ROM during push off (A2) (°)	2.6 ± 1.7	0.5	-4.8; 5.8	3.4 ± 1.6	2.2	-2.7; 7.1
Ankle dorsiflexion angle at IC (°)	3.6 ± 1.7	-2.8	-7.3; 1.7	5.5 ± 1.8	-4.6	-10.8; 1.6
Ankle plantarflexion angle at TO (°)	4.1 ± 1.3	1.9	-4.1; 7.9	6.1 ± 3.3	5.1	-1.7; 11.8
Peak ankle plantarflexion during GC (°)	4.3 ± 2.1	1.1	-6.9; 9.2	5.4 ± 2.9	4.6	-2.7; 11.9

Abbreviations: A1 = corresponding to A1 power phase of ankle; A2 = corresponding to A2 power phase of ankle; GC = gait cycle; H3 = corresponding to H3 power phase of hip; HR = heel rise; IC = initial contact;K1= corresponding to K1 power phase of knee; K2 = corresponding to K2 power phase of knee; K3 = corresponding to K3 power phase of knee; LoA = limits of agreement; LR = loading response; MSt = mid-stance; PLHIV = people living with HIV-1-infection; RMSE = root-mean-square error; ROM = range of motion; SD = standard deviation; SNP = HIV-seronegative participants; TO = toe-off; TSt = terminal stance.

6.2.2.2. Calibration-adjusted output comparison

Removing the calibration-offset between the kinematic waveforms of the systems/models resulted in improved consistency between systems/models regarding discrete angles, while ROM values were not affected. These results are presented in Table 6.3

In PLHIV, the biggest discrepancies between systems were noted for peak knee flexion during stance (loading response) (RMSE 7.4° ± 4.5°; bias 6.1°), hip internal rotation ROM during the gait cycle (RMSE 5.7° ± 3.3°) and hip flexion ROM during the gait cycle (RMSE 5.5° ± 2.1°).

In SNP, the biggest differences were similarly observed for peak knee flexion during stance (loading response) (RMSE 8.8° ± 5.1°; bias 6.8°) and hip internal rotation ROM during the gait cycle (RMSE 5.2° ± 1.4°). Offset removal rendered all other differences below 5°, although most LoA for most differences exceeded 5° for at least one of the limits.

Table 6.4. Concurrent validity of myoMOTION-measured kinematic gait angles (calibration-adjusted). Analyses were performed separately in people living with HIV (PLHIV) and seronegative participants (SNP).

Kinematic angle	SNP			PLHIV		
	Offset	Agreement		Offset	Agreement	
	RMSE (mean ± SD	Bias	95% LoA	RMSE (mean ± SD)	Bias	95% LoA
Pelvis						
Pelvis tilt ROM during GC (°)	2.1 ± 1.1	2.0	-0.1; 4.1	2.9 ± 1.8	2.2	-2.2; 6.5
Peak pelvis anterior tilt during GC (°)	1.2 ± 0.5	-0.7	-2.6; 1.3	1.8 ± 1.4	-0.4	-4.8: 4.0
Pelvis obliquity ROM during GC (°)	2.4 ± 1.7	-0.6	-6.2; 5.0	4.7 ± 3.3	1.7	-9.3; 12.7
Pelvis rotation ROM during GC (°)	3.3 ± 1.7	3.0	-0.6; 6.6	4.1 ± 2.4	3.7	-1.2; 8.6
Pelvis rotation at IC (°)	2.2 ± 1.0	0.6	-0.7; 1.8	1.8 ± 1.1	0.8	-0.9; 2.4
Hip						
Hip flexion ROM during GC (°)	3.5 ± 1.1	-3.1	-6.0; -0.2	5.0 ± 2.1	-5.0	-9.1; -1.0
Hip flexion ROM during LR (°)	1.9 ± 1.5	0.5	-1.3; 2.3	2.3 ± 1.3	1.3	-2.0; 4.6
Hip flexion ROM, PS to IS (H3) (°)	3.1 ± 1.4	<0.0	-5.2; 5.1	5.1 ± 4.4	-1.6	-10.4; 7.2
Hip flexion angle at IC (°)	4.1 ± 1.5	-3.7	-6.7; -0.6	4.9 ± 2.6	-3.9	-10.6; 2.8
Peak hip flexion during swing (°)	2.4 ± 1.7	-2.0	-5.4; 1.3	4.7 ± 1.9	-3.5	-9.7; 2.8
Peak hip extension during stance (°)	2.4 ± 0.7	-1.0	-4.7; 2.4	3.3 ± 3.0	-1.5	-9.1; 6.0
Hip abduction ROM during mid-stance (°)	3.2 ± 1.7	<0.0	-5.3; 5.4	4.5 ± 3.1	3.3	-3.1; 9.6
Hip adduction ROM during loading response (°)	3.2 ± 1.4	2.8	-0.1; 5.6	2.9 ± 1.9	2.5	-1.4; 6.3
Hip internal rotation ROM during GC (°)	5.2 ± 1.4	1.7	-6.0; 9.5	5.7 ± 3.3	2.7	-6.7; 12.1
Knee						
Knee flexion ROM during GC (°)	2.2 ± 0.9	0.4	-3.1; 3.9	3.0 ± 1.5	1.4	-3.3; 6.0
Knee flexion ROM during stance (K1) (°)	2.8 ± 1.3	1.6	-1.9; 5.1	1.9 ± 1.7	0.7	-2.0; 3.4
Knee flexion ROM from stance to swing (K3) (°)	2.5 ± 1.3	-1.7	-5.1; 1.6	2.6 ± 1.3	-1.5	-5.5; 2.5

Knee extension ROM, MSt to TSt (K2) (°)	2.5 ± 1.3	-2.1	-4.9; 0.7	3.4 ± 1.8	-3.0	-6.7; 0.6
Knee flexion at IC (°)	4.2 ± 1.7	-1.6	-7.8; 4.6	3.9 ± 1.9	-1.5	-7.2; 4.2
Peak knee flexion during stance, LR (°)	8.8 ± 5.1	6.8	-2.8; 16.3	7.4 ± 4.5	6.1	-3.4; 15.5
Peak knee extension during stance (°)	3.2 ± 1.2	-0.9	-4.2; 2.4	3.9 ± 2.1	-0.3	-7.1; 6.5
Peak knee flexion during swing (°)	2.4 ± 1.1	0.2	-3.7; 4.2	2.6 ± 2.2	0.4	-5.5; 6.3
Ankle						
Ankle dorsiflexion ROM during stance (A1) (°)	2.7 ± 1.1	2.0	-1.1; 5.2	2.7 ± 0.7	1.7	-1.5; 4.9
Ankle dorsiflexion ROM during swing (°)	2.3 ± 1.8	1.1	-3.3; 5.4	2.4 ± 1.0	1.1	-2.3; 4.6
Ankle plantarflexion ROM during push off (A2) (°)	2.6 ± 1.7	0.5	-4.8; 5.8	3.4 ± 1.6	2.2	-2.7; 7.1
Ankle dorsiflexion angle at IC (°)	3.4 ± 1.3	-1.6	-5.9;2.8	2.8 ± 1.8	-1.3	-4.2; 1.7
Ankle plantarflexion angle at TO (°)	2.8 ± 1.4	0.7	-3.7; 5.1	3.7 ± 1.9	1.7	-2.7; 6.0
Peak ankle plantarflexion during GC (°)	3.2 ± 1.6	-0.1	-5.5; 5.4	2.5 ± 1.9	1.2	-3.7; 6.1

Abbreviations: A1 = corresponding to A1 power phase of ankle; A2 = corresponding to A2 power phase of ankle; GC = gait cycle; H3 = corresponding to H3 power phase of hip; HR = heel rise; IC = initial contact;K1= corresponding to K1 power phase of knee; K2 = corresponding to K2 power phase of knee; K3 = corresponding to K3 power phase of knee; LoA = limits of agreement; LR = loading response; MSt = mid-stance; PLHIV = people living with HIV-1-infection; RMSE = root-mean-square error; ROM = range of motion; SD = standard deviation; SNP = HIV-seronegative participants; TO = toe-off; TSt = terminal stance.

6.3. MyoMOTION reliability

6.3.1. Temporal, spatial, temporophasic and temporospatial parameters (TSPs)

Table 6.5 presents reliability results for myoMOTION-measured TSPs in terms of SEM, %SEM and the upper 95% CL of the SEM. For spatial parameters, measurements in SNP demonstrated better reliability relative to PLHIV (lower SEM, %SEM and upper 95% CL), although %SEM observed in the two respective groups were within 1.78% of each other. In both groups, step length (both absolute and normalised) showed good reliability (5% ≤ %SEM < 10.00%),[364] while stride length (both absolute and normalised) showed excellent reliability (%SEM < 5%).[364]

In contrast, to the trend observed for spatial parameters, temporal and temporophasic parameters showed better reliability in PLHIV than in SNP, especially for stance time in seconds. Based on %SEM, this outcome demonstrated good reliability in SNP, but excellent reliability in PLHIV. Step time in seconds and single support time in seconds showed good reliability in both groups, while double support time in seconds demonstrated sufficient reliability (10.00% ≤ %SEM < 20.00%).[364] The largest error in double support time likely to be observed in 95% of cases for both groups was still only 0.04 seconds.

Stance time as a percentage of the gait cycle showed excellent reliability in both groups, single support percentage showed good reliability in both groups and double support percentage showed sufficient reliability.

Temporospatial parameters were more repeatable in SNP, although differences in %SEM were within ~1% between groups. Gait (stride) speed demonstrated excellent reliability in both groups, but once normalised to leg length, reliability was good in SNP and just above the limit for sufficient in PLHIV. The largest error likely to be observed in 95% of cases for PLHIV was still only 0.05 m/s – this remains below 0.1 m/s, which is considered as a clinically significant threshold in various populations.[369]

Table 6.5. Within-session reliability of myoMOTION-measured TSPs. Reliability was assessed using direct myoMOTION model output.

Parameter	SNP			PLHIV		
	SEM	%SEM	Upper 95% CL	SEM	%SEM	Upper 95% CL
Spatial parameters						
Step length (cm)	4.01	6.09%	4.81	4.33	6.82%	5.20
Normalised step length	0.04	5.20%	0.05	0.05	6.98%	0.06
Stride length (cm)	3.20	2.46%	3.84	4.03	3.23%	4.84
Normalised stride length	0.04	2.65%	0.05	0.05	3.56%	0.06
Temporal parameters						
Cadence (steps/min)	8.31	7.08%	9.97	9.67	8.82%	11.60
Normalised cadence	2.45	7.04%	2.94	2.83	8.57	3.40
Stance time (sec)	0.06	9.78%	0.07	0.03	4.48%	0.04
Step time (sec)	0.04	7.70%	0.05	0.04	7.22%	0.05
Single support time (sec)	0.03	7.14%	0.04	0.03	6.91%	0.04
Double support time (sec)	0.03	15.23%	0.04	0.03	12.77%	0.04
Temporophasic parameters						
Stance time (%GC)	1.97	3.31%	2.36	1.60	2.63%	1.92
Single support time (%GC)	2.56	6.34%	3.07	2.49	6.32%	2.99
Double support time (%GC)	2.18	11.42%	2.62	2.30	10.71%	2.76
Temporospatial parameters						
Gait speed (m/s)	0.02	1.58%	0.02	0.02	1.75%	0.02
Normalised gait speed	0.04	9.20%	0.05	0.04	10.34%	0.05

Abbreviations: %SEM = absolute percentage SEM; 95%CL = 95% confidence limits of SEM; GC = gait cycle; PLHIV = people living with HIV-1 infection; SEM = standard error of measurement; SNP = HIV-seronegative participants.
Bold print indicates clinically significant values.
SEM 95% confidence limits were calculated using a sample-and-trial-specific multiplying factor of 1.2.[362]

6.3.2. Kinematic angles

Table 6.6 presents reliability results for myoMOTION-measured kinematic angles during gait. SEM values were generally very similar between both groups. In SNP, pelvis rotation at initial contact and ankle plantarflexion angle at toe-off were the only angles with reliability exceeding 5°, while in PLHIV, peak knee flexion in stance (i.e. during loading response) showed an SEM of 5.8°, with an upper 95% CL of 7.0°. Additionally, ankle plantarflexion angle at toe-off and peak ankle plantarflexion during the gait cycle both demonstrated an upper 95% CL of 5.3° in PLHIV (although SEM values were below 5.0°).

Table 6.6. Within-session reliability of myoMOTION-measured gait kinematics. Reliability was assessed using direct myoMOTION model output.

Anatomical angle	SNP		PLHIV	
	SEM	Upper 95% CL	SEM	Upper 95% CL
Pelvis				
Pelvis tilt ROM during GC	0.7	0.8	0.8	1.0
Peak pelvis anterior tilt during GC	1.1	1.3	1.2	1.4
Pelvis obliquity ROM during GC	0.9	1.1	1.1	1.3
Pelvis rotation ROM during GC	2.1	2.5	1.8	2.2
Pelvis rotation at IC	5.2	6.2	3.7	4.4
Hip				
Hip flexion ROM during GC (°)	2.4	2.9	2.1	2.5
Hip flexion ROM during LR (°)	1.7	2.0	2.6	3.1
Hip flexion ROM, PS to IS (H3) (°)	2.3	2.8	2.0	2.4
Hip flexion angle at IC (°)	2.4	2.9	2.1	2.5
Peak hip flexion during swing (°)	2.2	2.6	2.1	2.5
Peak hip extension during stance (°)	1.8	2.2	2.4	2.9
Hip abduction ROM during mid-stance (°)	2.6	3.1	2.0	2.4
Hip adduction ROM during loading response (°)	1.4	1.7	1.5	1.8
Hip internal rotation ROM during GC (°)	2.6	3.1	2.8	3.4
Knee				

Knee flexion ROM during GC (°)	1.4	1.7	2.2	2.6
Knee flexion ROM during stance (K1) (°)	2.9	3.5	2.5	3.0
Knee flexion ROM from stance to swing (K3) (°)	3.0	3.6	2.8	3.4
Knee extension ROM, MSt to TSt (K2) (°)	1.9	2.3	2.4	2.9
Knee flexion at IC (°)	3.0	3.6	3.2	3.8
Peak knee flexion during stance, LR (°)	3.9	4.7	5.8	7.0
Peak knee extension during stance (°)	2.9	3.5	3.1	3.7
Peak knee flexion during swing (°)	2.0	2.4	2.9	3.5
Ankle				
Ankle dorsiflexion ROM during stance (A1) (°)	2.0	2.4	1.9	2.3
Ankle dorsiflexion ROM during swing (°)	2.9	3.5	3.3	4.0
Ankle plantarflexion ROM during push off (A2) (°)	2.2	2.6	3.7	4.4
Ankle dorsiflexion angle at IC (°)	2.0	2.4	2.1	2.5
Ankle plantarflexion angle at TO (°)	5.2	6.2	4.4	5.3
Peak ankle plantarflexion during GC (°)	4.1	4.9	4.4	5.3

Abbreviations: %SEM = absolute percentage SEM; 95%CI = 95% Confidence Interval; A1 = corresponding to A1 power phase of ankle; A2 = corresponding to A2 power phase of ankle; GC = gait cycle; H3 = corresponding to H3 power phase of hip; HR = heel rise; IC = initial contact; K1= corresponding to K1 power phase of knee; K2 = corresponding to K2 power phase of knee; K3 = corresponding to K3 power phase of knee; LoA = limits of agreement; LR = loading response; MSt = mid-stance; PLHIV = people living with HIV-1-infection; RMSE = root-mean-square error; ROM = range of motion; SD = standard deviation; SEM = standard error of measurement; SNP = HIV-seronegative participants; TO = toe-off; TSt = terminal stance.

6.4. Chapter summary

This chapter concludes the validity and reliability testing of the myoMOTION system. Results confirm that the validity of myoMOTION measurements was not compromised in PLHIV and community-matched SNP, and that findings (trends) were similar in both participant groups. Biomechanical modelling offsets between systems only affected discrete kinematic angles (pelvis, hip, knee and ankle), while TSPs and kinematic ROMs (with the exception of hip internal rotation ROM) were not affected and demonstrated values corresponding to good validity and reliability for direct myoMOTION modelling output. In addition, SEM values were similar to those obtained using the myoMOTION in healthy student volunteers (Study One) and similar to or smaller than published values for OMC systems.[318,326] All kinematic outcomes and TSPs showed clinically acceptable (kinematic differences < 5°) or acceptable-to-excellent (TSP percentage differences generally below 3%, and all below 20%) within-session reliability. For kinematic angles, total ROM in a given movement plane was generally more reliable than discrete angles. Apart from four discrete angles (pelvis rotation at initial contact, ankle plantarflexion at toe-off, peak ankle plantarflexion during the gait cycle and peak knee flexion during stance), reliability was clinically acceptable for all gait outcomes.

In summary, the myoMOTION proved a valid system for measuring the gait outcomes of interest in a South African rural cohort including PLHIV and SNP. In addition, because absolute reliability statistics such as the SEM provides results in the original unit of measurement, the measurement error for each of the outcomes to be analysed in the cross-sectional field study is now known and will aid data interpretation in the cross-sectional field study, presented in the next two chapters.

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PART III

DESCRIBING GAIT, BALANCE AND PHYSICAL PERFORMANCE IN SOUTH AFRICAN ADULTS LIVING WITH HIV-1 INFECTION

Preface

Part III of the dissertation reports the methodology and results of an observational cross-sectional study (with an analytical component) to address the main aim of the dissertation: the comparison of gait kinematics and postural balance of PLHIV to those of community-matched SNP to ascertain key biomechanical differences, and the determination of correlations between clinical physical performance tests and a gait summary score (based on valid quantitative outcomes), fall-related outcomes and self-reported function. Significant correlations with the gait score will validate the tests as being able to screen for quantitative, early changes locomotor impairments, while associations with self-reported function and fall-related outcomes will additionally indicate the potential to screen for consequences such as an increased fall risk. This third primary study is spread over two chapters (Chapters 6 and 7, see Figure below). Chapter 7 presents the study methodology, while Chapter 8 presents the results of both the descriptive comparison and correlation components of the study.

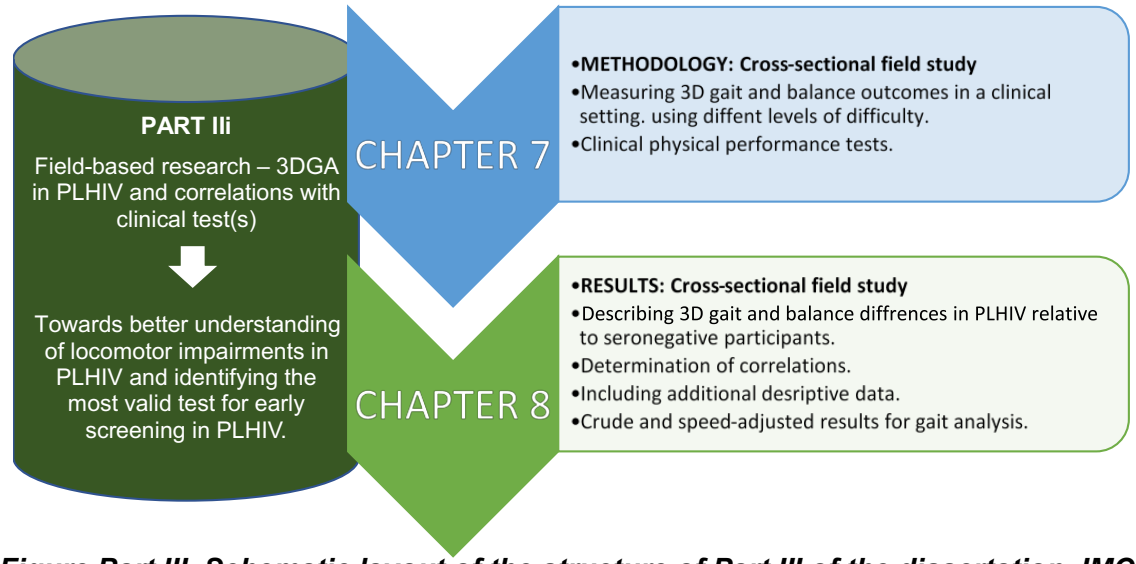

Figure Part III. Schematic layout of the structure of Part III of the dissertation. IMC = inertial motion capture; PLHIV = people lving with HIV-1 infection; TSPs = temporal and spatial parameters.

PART III

CHAPTER 7
METHODOLOGY: CROSS-SECTIONAL FIELD STUDY

7.1. Aims and objectives

7.1.1. Aim

The aim of this study was to describe gait and balance impairments existing among PLHIV residing in the Cape Winelands District of the Western Cape, South Africa, using state-of-the-art three-dimensional gait analysis (3DGA) technology. It further aimed to identify whether relationships exist between selected physical performance tests (which may be considered in clinical practice to screen for early functional decline in PLHIV) and the findings of 3D gait analysis (summarised using a quantitative gait score), self-reported function and history and fear of falling.

7.1.2. Objectives

PRIMARY:

1. To describe the difference in gait biomechanics between PLHIV and SNP as determined by pelvis, hip, knee and ankle joint/segment angles and angular motion during pre-specified key events and sub-phases and of the gait cycle under usual-paced, fast-paced and dual task conditions;
2. To describe the difference between PLHIV and SNP regarding static postural stability as determined by centre of pressure (COP) excursion and velocity during single leg stance;
3. To ascertain the correlations between clinical physical function test performance and a quantitative gait measure (i.e. a summary score of gait based on valid 3D-analysis gait outcomes), self-perceived functional ability, and fall-related outcomes (fall history, number of falls over the past year and fear of falling) within PLHIV.

SECONDARY:

1. To describe the difference in clinical physical function test performance between PLHIV and SNP as determined by scoring the Health ABC Physical Performance Battery (PPB), six-metre walk tests, single leg stance tests and chair rise tests.

7.2. Ethical considerations

The study was conducted in accordance with the Declaration of Helsinki. Ethical approval for this project as a sub-study to the EndoAfrica study[vi] was obtained from the Health Research Ethics Committee (HREC) of the Stellenbosch University (SU), South Africa (N15/05/043) (Appendix A). Permission to conduct the study at both the selected healthcare facilities of the Provincial Government of the Western Cape was provided by the Western Cape Provincial Research Health Committee (WC_2016RP10_878) (Appendices B and C). All eligible participants were required to read and sign an informed consent document prior to participating in the study (in their preferred language, English, Afrikaans or Xhosa). To ensure anonymity, a unique study identification code (e.g. HIVP2_001, HIVP2_002, etc.) was allocated to each participant on recruitment.

7.3. Study design

The research design was that of an observational, descriptive cross-sectional study, with correlation analysis incorporated as an analytical component. The project was a sub-study to the ongoing larger longitudinal EndoAfrica cohort (described previously in Chapter 4, Section 4.7.2).

7.4. Study setting

This study was conducted in Worcester and Paarl; two of the largest towns in the Cape Winelands district, Western Cape, South Africa (Figure 7.1). In each town, a public community health centre (CHC) was the research base: in Worcester, data collection was conducted in a dedicated, private room on a satellite SU medical campus (Ukwanda) directly adjacent to the Worcester CHC (due to restricted space in the CHC itself); in Paarl, data collection was conducted in a dedicated, private room in the rehabilitation wing of the TC Newman CHC.

[vi] *Cape Winelands HAART to HEART (Prevalence)/EndoAfrica study, Department of Physiological Sciences, Stellenbosch University/Division of Medical Physiology, Faculty of Medicine and Health Sciences, Stellenbosch University (N12/12/086).*

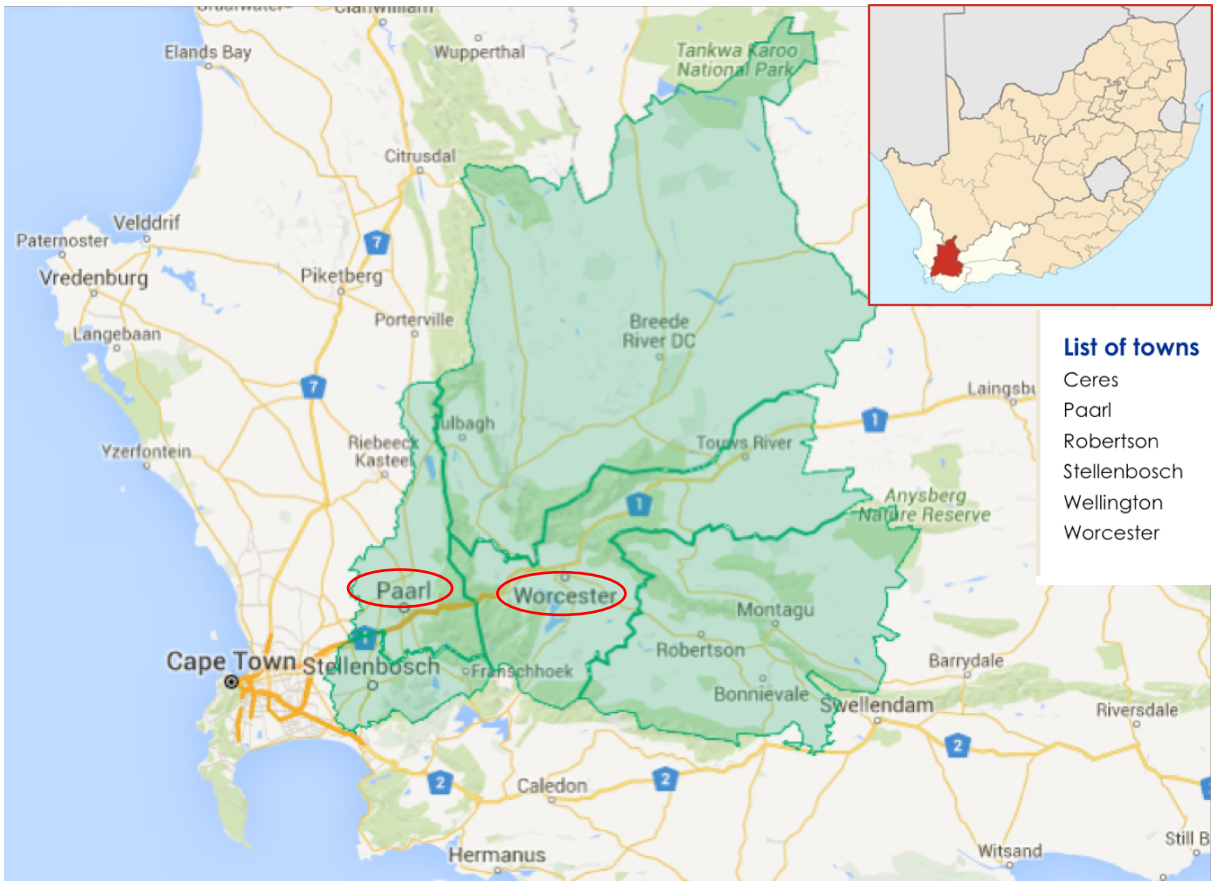

Figure 7.1. The Cape Winelands District (shaded red on the small and green on the larger map) of the Western Cape, South Africa. The current study was conducted in the towns of Worcester and Paarl, two of the largest towns in this municipal district.

7.5. Study population

Participants were recruited from the same population described for the overhead EndoAfrica study, as presented in Chapter 4, Section 4.7.2. For this sub-study, participants were additionally recruited from a former primary care site utilised by the overhead study, based in Paarl, to result in an additional but similar recruitment population. The study population primarily consisted of male and female adults (patients and their family or friends) residing in and around the Cape Winelands towns of Worcester and Paarl, Western Cape, South Africa, and visiting two public primary care CHCs in these regions. Both these sites represent primary care HIV clinics situated in two of the largest towns in the Cape Winelands District municipal area.

7.6. Sampling method

7.6.1. Sample size

Sample size was based on the study objective of testing the null hypothesis of equality of means in kinematic angles in two independent groups (PLHIV and SNP). A sample size calculation was performed based on preliminary data collected from the first 30 study participants (15 PLHIV and 15 SNP) in the field study, as no literature exists regarding expected effect sizes and variances of lower limb kinematics in PLHIV. A biostatistician was advised and recommended this pragmatic approach, which was stated as such in the study protocol. The following parameters were of interest for sample size calculation: absolute allowable error (minimum clinically important difference, MCID) in the estimation, the pooled standard deviation of the variable of interest (kinematic angles), statistical significance and statistical power.[370] MCID guidelines for lower limb kinematic parameters have been suggested in the literature with a threshold of 5° generally being deemed acceptable for instrumented gait analysis.[318,327,371] Results from the methods comparison studies (Part II of the dissertation) confirmed this value for IMC-measured gait when using the myoMOTION system in PLHIV. Preliminary kinematic results were examined to determine the outcome with the highest SD (inter-subject variability), which was identified as ankle dorsiflexion at initial contact. This allowed for a conservative estimate; consequently, the calculated sample size should be large enough to detect differences of 5° in lower limb gait kinematics. The pooled SD (δ) was calculated as:

$$\delta = \sqrt{\frac{(n_1 - 1)(s_1^2) + (n_2 - 1)(s_2^2)}{(n_1 + n_2 - 2)}}$$

$$= \sqrt{\frac{(15 - 1)(8.046^2) + (15 - 1)(8.693^2)}{(15 + 15 - 2)}}$$

$$= 8.376$$

where δ is the pooled SD, n_1 and n_2 are the sample sizes in the groups being compared, and s_1 and s_2 are the respective sample SDs.

Statistical level of significance was set at α = 0.05 (5% chance of finding a Type 1 error), and power (1-β) = 0.80 (20% chance of finding a Type 2 error). Sample size was subsequently calculated as:

$$N \geq \frac{2\delta^2\left(Z_{1-\alpha/2} + Z_{1-\beta}\right)^2}{D^2}$$

$$\geq \frac{2\,(8.376)^2(1.96 + 0.84)^2}{5^2}$$

$$\geq 44.003$$

where N is the minimun sample size per group, δ is the pooled SD, $Z_{1-\alpha/2}$ is the value from the standard normal distribution holding $1-\alpha/2$ below it (i.e. corresponding to significance of 0.05), $Z_{1-\beta}$ is the value from the standard normal distribution holding $1-\beta$ below it (i.e. corresponding to 0.80 power) and D is the MCID.

A total sample of at least 45 participants per group was thus proposed to detect a difference of 5° in joint angles. An additional 10% of participants were considered to allow for potential missing data points, resulting in a sample size of 50 participants per study group.

A *post hoc* power analysis was performed to ascertain the power of the sample size of 50 PLHIV to detect a moderate correlation (r = 0.4) between clinical performance tests and enhanced Gait Variability Index (EGVI) scores (the main criterion for validating the performance tests). Power was determined as 83%, which is deemed sufficient (>80%).

7.6.2. Eligibility criteria

Apart from the specific criteria related to HIV-serostatus (see Sections 7.6.2.2 and 7.6.2.3 below), participants were selected on the basis of similar eligibility criteria:

7.6.2.1. General criteria

General eligibility criteria were similar to those listed for the second validity and reliability study, as listed and motivated in Section 4.8.1. Briefly, participants were eligible for the cross-sectional field study if they were:

1. Adults (aged 18 to 65 years).
2. Had a body mass index (BMI) < 25kg/m^2.
3. Were independently ambulant (without any walking aids).
4. Were able to consent and participate in all study procedures.

Participants were excluded if they:

1. Were pregnant (if female).

2. Had a current acute opportunistic infection or illness.
3. Suffered from distal sensory peripheral neuropathy (data from folder and/or self-report; confirmed via a brief neurological conduction examination performed by the researcher).
4. Had a history of seizures, mental retardation, head injury, stroke, epilepsy, cerebral palsy or other major neurological conditions.
5. Suffered from any other neuromusculoskeletal impairments or injury that might affect their usual gait.
6. Were visually impaired (not correctable with spectacles or contact lenses).
7. Had ingested alcohol on the day of testing.

7.6.2.2. Criteria for the HIV-seropositive group

1. For the HIV-1 seropositive group (PLHIV), participants had to have a confirmed diagnosis of HIV-1 infection via blood test, either as an already-enrolled participant in the EndoAfrica study or as a participant independently recruited for the biomechanical sub-study. Once screened for the present study by the research nurse or health practitioner, and after agreeing to having their blood tested, those individuals who did not already have their status confirmed as part of the EndoAfrica study, were counselled by the research nurse (Worcester) or HIV-counselor (Paarl) and a rapid HIV test was performed at the relevant CHC to confirm their status.
2. PLHIV were included regardless of HAART use. The systematic review[62] presented in Chapter 3 found that gait and balance impairments in PLHIV is not likely associated with HAART use.

7.6.2.3. Criteria for the HIV-seronegative group

1. For the HIV-seronegative comparison group (SNP), participants had to be HIV-seronegative adults from the same community as the HIV-1 seropositive group (either EndoAfrica participants or not). Once screened by the research nurse or health practitioner, and after agreeing to having their blood tested, those individuals who did not already have their status confirmed as part of the EndoAfrica study, were counselled and a rapid HIV test was performed at the CHC to confirm their status.

7.6.3. Sampling procedure

All participants fulfilling eligibility criteria were recruited consecutively until the required sample size for this study was achieved. Although it may not be assumed that this method of sampling results in a fully representative sample of the entire target population, consecutive sampling was deemed the most appropriate option within the time- and financial constraints of the project. This method is also considered the best option among nonprobability techniques, as all available participants fulfilling inclusion criteria are studied, resulting in a fairly good representation of the overall population in a reasonable time frame.

The sample of 100 adults (50 PLHIV and 50 SNP) was recruited from Worcester and Paarl between June 2016 and December 2017. Figure 7.2 illustrates the eligibility criteria and recruitment of study groups. Participants were enrolled from a local CHC in each respective town, making use of Health Professions Council of South Africa (HPCSA)-registered nurses (Worcester and Paarl) and accredited HIV-counsellors (Paarl). At the Worcester site, participation was proposed consecutively to individuals already enrolled in the EndoAfrica study or patients and their friends and family attending the CHC, identified by the nurse as potential participants (in the same manner as recruiting participants for the EndoAfrica study). At the Paarl site, PLHIV receiving primary outpatient care at TC Newman CHC and who were potentially eligible, were consecutively referred for study participation by the attending medical practitioner or nursing sister. Potentially eligible SNP were referred by the accredited HIV counsellors (who are also responsible for HIV testing) at the Paarl clinic. This ensured that these participants already had supporting blood results, fulfilling one of the criteria to participate as a control.

At both sites, the relevant health professionals explained study procedures to potential participants, including the need for HIV-testing as part of the eligibility criteria. At the Worcester site, the research nurse also performed eligibility screening. Upon attending their scheduled session for data collection, participants had the chance to further discuss any questions or concerns with the researcher and still had the opportunity to decline participation. At the Paarl site, the researcher performed eligibility screening (referred participants had their HIV-serostatuses already confirmed). Data collection sessions, either at the SU Ukwanda campus (Worcester) or in a dedicated room in TC Newman (Paarl), were scheduled on the same day of recruitment if participants indicated that they had time available (participants often had taken the entire day off from work to allow for visiting the CHC). For participants awaiting medication from the clinic pharmacy, arrangements were made to have these medications prepared for collection by the participant directly after their study participation. Alternatively, if

participants had other commitments, a suitable date and time was scheduled for data collection at the participant's convenience and written on an appointment card. For those with mobile phones, a reminder text message was sent the day before participation, or the research nurse contacted their home phones. In Worcester participants were transported between the CHC and the SU Ukwanda campus, located directly next to Worcester CDC, by the research team (either the PhD candidate or a research assistant). All participants who still needed their serostatuses confirmed had to specifically provide signed informed consent for (and prior to) HIV screening – either as part of EndoAfrica consent or on the specific consent form for this study. Informed consent forms for this study were separate from the EndoAfrica forms and specific to each clinic (Appendices F and G). At both research sites, all participants received compensation for inconvenience and their time spent on research activities at a rate as recommended by the National Health Research Ethics Council (NHREC),[334] provided in the form of local supermarket food vouchers.

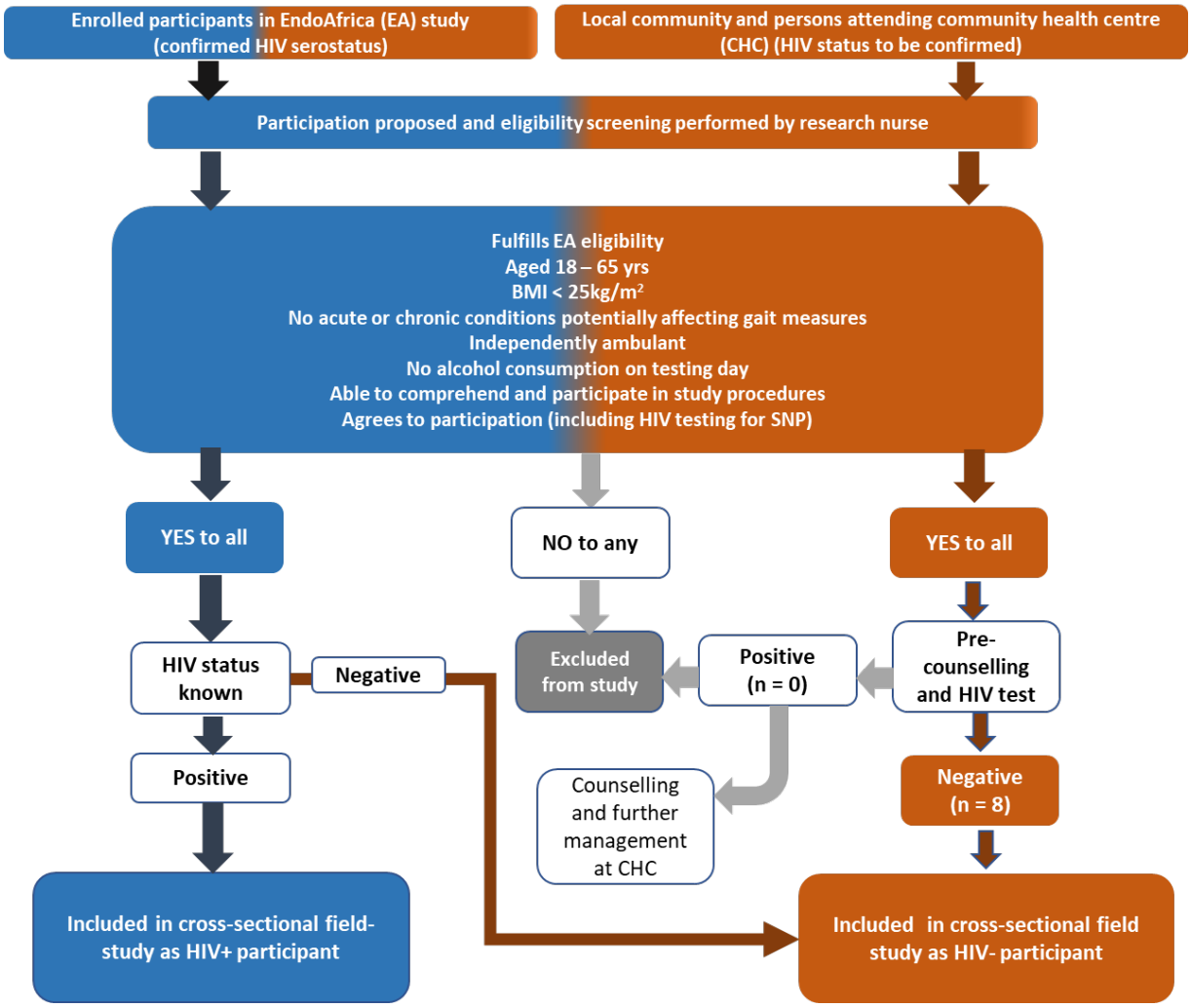

Figure 7.2. Flow chart demonstrating sample recruitment for the cross-sectional field study.

7.7. Measurement instruments and outcomes

7.7.1. Three-dimensional gait analysis

The myoMOTION inertial motion capture (IMC) system was used to capture walking gait biomechanics of the participants. The system was described in detail in Chapter 4, Section 4.10. The 28 pelvic, hip, knee and ankle kinematics and 15 TSPs that were evaluated in the validity and reliability studies (described in Tables 4.5 and 4.6) were measured. Most of these outcomes demonstrated clinically acceptable reliability in the laboratory-based studies reported in Chapters 5 and 6. However, four discrete kinematic angles (ankle plantarflexion at toe-off, peak ankle plantarflexion during the gait cycle, peak knee flexion during stance and pelvis rotation at initial contact) demonstrated clinically unacceptable absolute reliability (Table 6.6). Although these angles were retained in the analyses to aid visualisation of the overall gait pattern, they were flagged as outcomes that cannot be considered to represent a true between-group difference or true descriptors of gait in PLHIV. These four angles were thus not interpreted as contributors to the gait pattern.

7.7.2. Composite score for quantifying gait variability (the enhanced Gait Variability Index, EGVI)

The enhanced Gait Variability Index (EGVI) is a single-score summary measure used to quantify gait variability and is linked to mobility function.[372,373] Specifically, it quantifies the distance between the magnitude of variability in a normative reference group, and that in a patient group.[372] The index is based on five TSPs which are associated with functional outcomes (such as fall risk).[238,372,374,375] When used in older adults (≥ 65 years old) and across a range of mobility limitations and functional abilities (including high functioning individuals who may have had similar variability to the healthy reference population),[372] the EGVI could discriminate elders with increased as well as decreased gait variability. The EGVI demonstrated significant ($p<0.05$) and moderate to strong correlations (r between 0.5 and 0.7) with all clinical tests of balance and mobility used in the study, and demonstrated a significant but weak correlation with history of falls ($r = 0.35$; $p < 0.05$). In addition, the index has been recommended[372] as a more appropriate alternative to its predecessor (the original Gait Variability Index, GVI[375]) (A. Gouelle 2018, personal communication, 12 July).

In this study, the validity and reliability of the individual parameters used to calculate the EGVI (step length [cm], step time [s], stance time [s], single support time [s], and stride velocity

[cm/s]) was confirmed in PLHIV and SNP (Chapter 6). Therefore, although properties such as minimum clinically important difference (MCID) and discriminant validity of the EGVI in PLHIV remains unknown at this stage, the index was deemed justifiable as a valid summary measure of gait in this study.

An EGVI score of 100 is considered "normal", as it represents the mean score for the reference group. Obtaining a score of 100 would thus indicate that the relevant individual has an amount of variability that is similar to the norm, with each 10-point difference indicating a one standard deviation (SD) removal from the norm. A score greater than 100 indicates increased gait variability (e.g. a more unstable gait), and a score below 100 indicates reduced variability relative to the norm (e.g. a more rigid gait).[372] Although existing control group values are embedded in the EGVI and is available for use, these data were obtained from French adults and would not be suited as reference data for this study cohort of younger-to-middle-aged adults from a rural South African community. The EGVI allows for replacing the embedded reference values with custom norms, and therefore data from the SNP (usual-paced walking) in this study were used to determine the normative EGVI values.

7.7.3. Static balance

Instrumented analysis of static standing balance was conducted using a high-resolution dynamic pressure mapping device, the MatScan Versatek (sensor model 3150E, Tekscan, Boston, Massachusetts) (Figure 7.3) at a frequency of 400 Hz. The MatScan is a low profile floor mat (thickness of 0.6 cm) comprising 2288 resistive sensors (1.4 sensors/cm^2) with a sampling frequency of up to 440 Hz.[376] Measures of anteroposterior (AP) and mediolateral (ML) sway can be provided by the device, including area and direction, elliptical pattern, distance and direction travelled by the centre of force (COF), variability in distance travelled by the COF, weight-bearing percentage and pressure distribution profiles.[377] For this study, six COP-based measures were analysed[378] (see Table 7.1 for descriptions and equations). The MatScan is portable and easy to operate, and is routinely used in clinical and research settings,[379] including middle-aged HIV-1 seropositive populations.[323,324] The validity of the MatScan for measuring COP parameters has been reported in healthy individuals as well as in various patient populations. Specifically relating to single leg standing, the MatScan has proven to provide valid COP measurements relative to force plate data during eyes open (EO) and eyes closed (EC) conditions in healthy adults ($r > 0.92$, $p < 0.001$).[320] Measurement error for COP measures using the MatScan has only been reported in elderly rheumatoid arthritis

patients, with values of 1.29 mm to 1.33 mm being reported for ML displacements, and 1.79 mm to 2.35 mm for AP displacements.[379]

Figure 7.3. The MatScan pressure mat.

Table 7.1. Centre of pressure (COP) parameters assessed in the cross-sectional field study.

Parameter	Description	Equation[378]
Mean COP velocity (mm/s)	Total COP excursion (distance travelled) for the specified time period, divided by the time period.	$MVELO = TOTEX \div T$
Mean COP velocity in AP direction (mm/s)	Average velocity of the COP in the AP direction	$MVELO_{AP} = TOTEX_{AP} \div T$
Mean COP velocity in ML direction (mm/s)	Average velocity of the COP in the ML direction.	$MVELO_{ML} = TOTEX_{ML} \div T$
Mean COP distance (mm)	Average distance from the mean COP (mean of the RD time series).	$MDIST = 1 \div N \sum RD[n]$
Mean COP distance in the AP direction	Average AP distance from the mean COP (mean absolute value of the AP time series)	$MDIST_{AP} = 1 \div N \sum \lvert AP[n] \rvert$
Mean COP distance in the ML direction	Average ML distance from the mean COP (mean absolute value of the ML time series)	$MDIST_{ML} = 1 \div N \sum \lvert ML[n] \rvert$

Abbreviations: AP = anteroposterior (forwards/backwards); COP = centre of pressure; ML = mediolateral (sideways); mm = millimetres; mm/s = millimetres per second; MVELO = mean COP velocity; N = number of data points in analysis; n = time series (1,…,N); RD = resultant distance time series, referring to the vector distance from the mean COP to each pair of points in the AP_o and ML_o time series, where the AP_o and ML_o time series defines the COP path relative to the origin of the pressure mat coordinate system; T = period of time selected for analysis (30 seconds); TOTEX = total excursion of COP (total length of COP path).

7.7.4. Physical performance tests

Table 7.2 summarises the functional components assessed in this study by the various physical performance tests as well as the self-reported questionnaire.

Table 7.2. Aspects of functional impairment and activity limitations assessed by the physical performance tests and the self-reported outcome measures.

Physical performance test	Aspect assessed
The Health ABC Physical Performance Battery (PPB)	Static balance, mobility and dynamic balance at a higher level of the functional spectrum compared to the SPPB.
The Single Leg Stance Test	Static postural balance and ability to shift weight into single support.
The Six-metre Walk Test	Gait speed (usual-paced) over a short distance.
The 5STS test	Lower limb muscle strength, speed and power, dynamic balance and functional mobility.
The 30sSTS test	Lower limb muscle strength and endurance.
Eyes closed conditions	Sensory reweighting; ability of vestibular and somatosensory systems to compensate lack of vision.
Dual task activities	Executive function; in particular related to divided attention (capacity to multi-task).[380]
Self-reported questionnaire	**Domain assessed**
The EQ-5D-5L mobility function domain	Self-perceived walking ability.
The EQ-5D-5L self-care function domain	Self-perceived ability to wash and dress one-self.
The EQ-5D-5L usual activities domain	Self-perceived ability to perform usual activities such as work, study, housework, family or leisure activities.

Abbreviations: 30sSTS = 30-seconds Sit-To-Stand; 5STS = Five-Times Sit-To-Stand; EQ-5D-5L = EuroQol 5-Dimensions 5-Levels questionnaire; PPB = Health ABC Physical Performance Battery; SLS = single leg stance; SPPB = Short Physical Performance Battery.

7.7.4.1. The Health ABC Physical Performance Battery (PPB)

Functional movement and balance in PLHIV and SNP were assessed using an expanded version of the traditional Short Physical Performance Battery (SPPB), namely the Health ABC Physical Performance Battery (PPB) (Appendix H). The original version of the SPPB[381] have previously been shown to be both adversely affected and associated with falls in PLHIV.[2,53,54,60,62] However, since the SPPB is an instrument established in the elderly, it may

be limited by a ceiling effect in younger people with higher functional performance levels.[53] Given that this study would include a relatively younger cohort, an expanded version of the SPPB was implemented to improve discrimination of physical function at the higher end of the functional spectrum, as proposed by Simonsick et al.[382] The PPB has been validated for repeated measures of physical performance in elders who are high-functioning.[382–384] The battery is scored according to standing balance (30-second positions held in a semi-tandem, tandem and SLS test), chair rise tests (the time taken to rise five times without assistance from sitting), gait speed (calculated in metres per second from the time taken to walk six metres at a usual pace) and a narrow walk test of dynamic balance (time to walk along a six-metre-long, 20-cm wide walkway).

PPB total score ranges continuously from zero to four. Higher scores indicate better performance. The first step in the scoring process is to convert test times to rates (speed) for the repeated chair stands (chair stands per second) and the two walk times (metres per second), and to assign a score of zero when a test was not done successfully. For standing balance, the time each of the three stands was held is summed, to create a maximum time of 90 seconds. Each test performance is then divided by a standard divisor representing the maximal performance possible on that specific test, to derive a ratio score ranging from zero to one.[382] For the chair stands, the divisor was 1x chair stand/second; for both the usual and narrow walks, the divisor was 2m/s; and for standing balance, the divisor was 90 seconds.[382] Finally, the ratio scores from the four individual tests are summed to generate a continuous scape ranging from zero to four. Simonsick et al.[382] designed this approach specifically to minimise ceiling effects and maximise overall dispersion on each measure. A change of 0.12 points on the PPB is considered to be a “small meaningful” change, while a difference of 0.22 is regarded as a “substantial” change.[385] The instructions for the PPB is presented in Appendix H. For the SLS component, the same instructions as in Section 7.7.4.2 below were used.

7.7.4.2. The Single Leg Stance (SLS) Test (eyes open, closed and dual task)

The single leg stance (SLS) test is commonly used to assess balance impairments and risk of falling across age groups.[386–389] The test is associated with fall risk, particularly injurious falls and it has been demonstrated that adults who are unable to hold the test for five seconds have 2.1 times the risk of sustaining an injurious fall.[279] It was one of the first clinical tests to be assessed objectively in PLHIV, although it is difficult to draw definite conclusions regarding impairment of this activity due to heterogeneous reporting of methodology and results.[62] Nonetheless, and despite some criticism of the test as having learning effects, it may be an

appropriate activity for challenging and evaluating equilibrium since SLS may be involved in various motor tasks (walking, dressing, turning, stair climbing stair climbing) which require a transition from bipedal to single-leg conditions.[390] Good test-retest reliability has been reported for the SLS in healthy women aged 55 to 77 years: intraclass correlation coefficients (ICC) ranged from 0.90 to 0.91 for eyes open (EO) and 0.74 to 0.75 for eyes closed (EC) conditions.[391] A higher score on the test (longer time held) indicates better function.

Although SLS with eyes open (EO) was assessed as part of the PPB, it was also performed separately on the pressure mat to enable capturing of centre of pressure (COP) data. In addition, trials were performed with EC and whilst performing a dual task. Participants were instructed to stand with both feet comfortably apart and facing forward on the pressure mat, with their arms crossed. Leg dominance does not seem to affect one-legged balancing ability[392] and participants were thus allowed to choose a preferred stance leg. On verbal command, they were to stand on one (the preferred) leg by lifting the opposite foot so that the foot is ankle-height off the ground, but not touching the other leg. Participants were instructed to look straight ahead and focus on a point in front of them on the wall (an image of a large cross was fixated at eye-level on a wall about three metres in front of the participant). The instruction was to hold the SLS position as still and for as long as possible without the lifted leg touching down, and without shuffling or hopping (weight-bearing foot to remain fixed on mat) and until the verbal command was given to stop (i.e. after 30 seconds).

Instructions for the SLS eyes closed (EC) condition were the same as for the EO condition, except that participants' eyes had to be closed as soon as they had lifted the foot and gotten in position, and to keep their eyes closed for the duration of the trial. The third SLS condition involved the addition of a dual task (DT) activity (see Section 7.7.4.5). The instructions were to start counting backwards on a verbal command, and then to lift the foot upon the second verbal command.

Participants were allowed a practice trial for all conditions, where after three test trials of 30 seconds each were conducted in a random sequence (including the walk trials for instrumented gait analysis) to account for potential fatigue or learning effects towards the end of the trials. The trials were timed with a stopwatch and the best time out of three performances was recorded. The reported MCID for the timed SLS varies widely, from 10.8 seconds[393] to 24.1 seconds.[394]

7.7.4.3. The Six-metre Walk Test (6mWT)

Gait speed is widely cited as a valid and reliable metric and predictor for functional status and overall health.[50] It is strongly associated with quality of life and has been called the "functional vital sign".[395] A meaningful change in gait speed has been established at 0.1 m/s (at usual pace over a short course) across various populations, including elderly, hip fracture, and others.[369] For the assessment of usual gait speed over a short distance, participants had to position themselves standing behind a starting line marked with masking tape on the floor; toes just touching the tape. The instruction was to start walking in a straight line upon the command "GO", and to perform this walk at their usual walking pace along the six-metre long walkway. Participants were instructed to keep walking for a few steps once crossing the line marking the end of the course. In addition to a single practice trial, two trials were performed and the faster of the two attempts was used for analysis in this study (the time taken to walk the six-metre course was converted to speed in metres per second).[396] This test formed part of the PPB, but an additional task condition was also performed, which involved a dual task activity (see Section 7.7.4.5). For this, participants were instructed to assume a standing position behind the starting line (as for the usual Six-metre Walk Test), to start counting (while still standing still) on a verbal command, and then to start walking whilst keeping on counting on the second verbal command. Participants were asked to count as accurately, not as fast, as possible without stopping their walk.

7.7.4.4. Chair rise tests: the Five-Times Sit-To-Stand (5STS) Test and the 30-second Sit-To-Stand (30sSTS) Test

Chair rise tests are measures of mobility-related function.[397] These tests are usually employed to evaluate older adults; however, it has also proven to be valid as a measurement of physical performance in healthy younger adults.[398] A systematic review[399] found that the Five-Times Sit-To-Stand (5STS) Test demonstrated good to high test-retest reliability (ICCs 0.64 to 0.96) in most populations, including younger and older community-dwelling adults. The 5STS test has been recommended for use in PLHIV, as performance in this patient group was observed to be significantly slower (worse) relative to normative results.[2,59]

STS was implemented both as a 5STS and a 30-second Sit-To-Stand (30ssts) Test. The two tests require execution of the same motion, but differ with regard to what they measure. The 5STS test assesses the time required to complete five rapid STS actions, while the 30sSTS test records the number of repeated STS actions that can be completed within a period of 30 seconds.[400] The two tests are not considered interchangeable as the 5STS test is an indication

of lower limb power and speed, whereas the 30sSTS test is a proxy measure of lower limb endurance.[400] MCIDs of two seconds have been reported for the 5STS test[3,401] and of two to 2.6 repetitions for the 30STS test.[402]

The 5STS test was conducted by measuring the time taken for the participant to stand up from a seated position, with arms folded across the chest, five times as fast as possible. The 30sSTS test, on the other hand, was conducted by asking the participant to perform as many as possible sit-to-stand manoeuvres for 30 seconds.[403] Both tests started with the participant seated with feet comfortably placed (knees close to 90°) and ended in a standing position.[404] A standard chair (seat height of 44.5 cm, Figure 7.4) with a stable backrest and solid seat was used for the test, according to the standard STS test protocol.[404,405] The tests were timed to a hundredth of a second using a stopwatch. Prior to the STS tests, two practice STS repetitions were allowed. The 5STS test was performed twice and the best result (fastest time) were used in this study for analysis[397] whilst the 30sSTS test was performed once considering the fatigue it may inflict. Standardised instructions for the 5STS is provided in Appendix H as part of the PPB.

Figure 7.4. The standard-height chair used for the chair rise tests, and layout of the narrow walkway.

7.7.4.5. Dual tasking

In order to investigate functional performance under more challenging conditions, participants additionally performed gait and balance tasks under dual task conditions. Dual tasking methodology is based thereon that performance of a more difficult, conscious activity interferes with a simultaneously performed primary task.[406] It is proposed that the performance difference between single- and dual tasks represent the demands on the processing system when attention is divided between two tasks simultaneously, and thus may be used as an

indication of the attention demands (cognitive compensation) required by the primary task.[187] In PLHIV, this might reveal more subtle movement impairments in higher functioning individuals.[62,186]

The cognitive task was fully explained to each participant, i.e. counting backwards aloud in a suitable numerical unit. Subsequently, the appropriate level of difficulty was determined during a seated practice round.[187] Participants were asked to count aloud backwards from a randomly selected number in units of three (practice started with this level), seven (if threes were deemed too easy), two (if threes were deemed too difficult) or one (if twos were deemed too difficult). The highest level of difficulty that the participant was able to perform as a single task was selected.[187] This methodology was deemed appropriated due to the expected variation in level of education in the population (from tertiary education to no schooling). Subsequently, participants performed the relevant clinical tests (as described above) with the addition of the cognitive task. The number of mistakes during each trial was noted and a Cognitive Difficulty Score (CDS)[187] was assigned (CDS data were not analysed for the purposes of this dissertation). The dual task performance sheet is attached as Appendix I.

7.7.5. Self-reported function (via the EuroQol Five-Dimension Five-Level questionnaire)

Participants were required to complete the entire five-level version of the European Quality of Life Five-Dimension questionnaire (EQ-5D-5L) (Appendix J), a standardised and extensively validated and tested instrument.[407] Three domains were analysed to represent self-reported function (see paragraph below), while the domains related to current pain and anxiety/depression were presented separately (the depression/anxiety domain was analysed as representing self-reported anxio-depressive symptoms; the acute pain domain was analysed as an indicator of pain on the day of testing). The health-related quality of life (HRQOL) visual analogue scale (VAS) data from the EQ-5D-5L were not analysed for the purposes of the current dissertation, but will be reported at a later stage.

The EQ-5D-5L was used to measure dimensions of subjective function as domains of HRQOL: specifically, the domains of mobility (walking), self-care (washing or dressing) and usual activities (e.g. work, study, housework, family or leisure activities). The EQ-5D-5L is available in English for South Africa, Afrikaans and isiXhosa and although not specifically designed for HIV-1 infection, has been validated, tested for reliability and successfully applied in PLHIV,[408–410] including in South African adult HIV-seropositive populations,[407,411,412] according to standards set by the EuroQol Group.[413] Delate and Coons[409] provide evidence for the

construct validity of the EQ-5D in PLHIV and report that the EQ-5D ($p < 0.05$) was able to discriminate between groups of participants stratified by disease severity on the basis of either CD4+ cell counts or HIV-1 RNA copies. The EQ-5D was introduced by the EuroQol Group in 2009 to improve the sensitivity and to reduce ceiling effects of the previous three-level instrument (the EQ-5D-3L). The EQ-5D-5L essentially consists of two pages: the EQ-5D-5L descriptive system and the EQ visual analogue scale (EQ VAS). The descriptive system defines health in terms of five dimensions or domains: mobility function, self-care function, usual activities function, pain and anxiety/depression. Each of the five dimensions comprising the EQ-5D descriptive system is divided into five levels of perceived problems: no problems, slight problems, moderate problems, severe problems and extreme problems. The participant is requested to indicate their current health state by ticking the box next to the most appropriate statement in each of the five dimensions, resulting in a one-digit number (between one and five) that expresses the level selected for that dimension. For analysis in this study, the EQ-5D-5L levels were dichotomised into "no problems" (i.e. level 1) and "problems" (i.e. level 2 to 5), in order to change the profile into frequencies of reported problems.[414]

7.7.6. Fall history and fear of falling

For this study, a fall was defined according to the definition posed by the Prevention of Falls Network Europe (ProFaNE) as "an unexpected event in which the participant comes to rest on the ground, floor, or lower level",[415] which has also been used in previous fall studies in PLHIV (see Table 2.1). The assessment of fall history (over the past 12 months) and fear of falling formed part of the self-administered questionnaire (Appendix K) and comprised of questions previously used in a South African Western Cape population.[416] The history of any, as well as the number of, fall(s) in the past year was assessed by using the questions, "Have you had a fall in the last year (by that, I mean did you fall to the ground, or to a lower level)?" and "If YES, about how many times did you fall in the last year?", respectively. Further inquiry was also made about the circumstance leading to the fall, since only falls *not* resulting from a major external event (such as pedestrian accident or having a stroke) were included in the study analysis. Additionally, all participants were asked about fear of falling ("Are you ever afraid of falling when walking or standing?" with a "yes" or "no" answer, and an inquiry into the reason for the fear of falling.

Although not yet investigated specifically in PLHIV, a review by Ganz et al.[417] found that simple retrospective recall of falls over the past year demonstrates similar specificity (specificity 91% to 95%) but less sensitivity (sensitivity 80% to 89%) than ongoing prospective weekly and monthly fall calendars or diaries. It remains uncertain as to what the optimal time period is to

assess using simple recall questions,[156] although it has been shown that falls recall in a one-year timeframe was better than shorter three- or six-month recall periods.[418] It has been suggested that for studies where intensive and prospective ascertainment of falls is not feasible, 12-month falls recall questions with fewer responses may be an acceptable alternative.[419] Falls were dichotomised as any ("yes") or none ("no") in the prior 12 months,[55,158] and the number of falls over this period was dichotomised as having had a single fall versus two or more falls.

7.7.7. Other questionnaire data and clinical measures

All participants completed a custom-designed baseline questionnaire (Appendix K). Before data collection, the questionnaire (and also the EQ-5D-5L questionnaire) was piloted on five PLHIV and five SNP from the same community and recruited in the same manner as other participants (these individuals participated in the validation study, for which questionnaire data were not relevant, and their data were thus also not analysed as part of the cross-sectional study). This was done to confirm sufficient understanding (face validity), i.e. to evaluate the appropriateness of questions and to allow correction of unclear items.

Apart from sociodemographic information, the questionnaires included questions pertaining to co-morbidities to augment folder information extracted from the EndoAfrica study. Participants who were not enrolled in the EndoAfrica study, were asked to complete an additional brief questionnaire (extracted from the formal EndoAfrica questionnaire – Appendix L).

7.7.7.1. Peripheral neuropathy and lower limb joint ROM screening

Although also included in the verbal screening, functional lower limb joint ROM and the absence of sensory peripheral neuropathy was confirmed via a brief screening. A goniometer was used to assess for any gross joint restrictions (as in Chapter 4, Section 4.11.2.1) while a brief neurological examination (ankle reflex and light touch) was performed to check for neuropathy. No additional participants had to be excluded following these confirmatory tests.

7.7.7.2. Clinical and anthropometric characteristics

Height was measured with the participant barefoot and in light clothes, by having the participant stand straight on the floor with their heels, back and head against a wall and arms hanging freely by their sides. A flat, rigid measuring ruler was placed horisontally on the participant's head and the point where it touched the wall was marked. The vertical distance

from the mark to the floor was then measured with a tape measure, and recorded in centimetres to the nearest 0.5 centimetre.[416] The use of a stadiometer was preferable to measure standing height, but due to budgetary constraints, was not feasible for the study. Weight was measured using an electronic scale as described in Chapter 4, Section 4.11.2.2.

7.7.7.3. Muscle strength

Hand-held dynamometry (HHD) offers an affordable, portable, and easy-to-use alternative to laboratory-based dynamometry for the assessment of isometric muscle strength, and has previously demonstrated excellent results for use as a clinically-feasible tool.[420–422] Lower limb muscle testing was performed using a Lafayette Manual Muscle Testing System Model-01165 (Lafayette Instrument Company, Lafayette IN, USA). This particular model has demonstrated good to excellent reliability for most measures of isometric lower limb strength in a healthy population, with intra-rater reliability proving good to excellent (ICC $\geq$ 0.75) (highest values having been obtained for proximal muscles).[420] Concurrent validity (criterion-reference: Kin-Com dynamometer) was good to excellent for the hip and knee (ICCs $\geq$ 0.75), with mostly moderate results shown for the ankle muscles (ICCs $\geq$ 0.51).[420] In addition, in a South African population of PLHIV, intra- and interrater reliability of HHD was demonstrated as good, with r-values for hip flexors ranging between 0.94 to 0.97, for knee extensors between 0.83 to 0.90 and for ankle dorsiflexors between 0.76 to 0.89.[422] Having used a hand-held dynamometer (HHD) before (e.g. undergraduate class demonstrations) the researcher (PhD candidate) was familiar with the device and its operation.

In this study, the maximal isometric strength of the hip flexors, extensors and abductors; knee flexors and extensors; and ankle dorsi- and plantarflexors was assessed using a make test. Make tests are reported to be more reliable, comfortable and safe than break tests[423] and require the examiner to hold the HHD stationary while the subject exerts a sustained maximal force against it. In contrast, a break test is performed when the participant's maximal muscular effort is overcome by the examiner and the tested joint gives way.[423] The testing positions for each participant were standardised to ensure that gravity eliminated positions were used for each muscle group. In order to avoid participant fatigue due to frequent position changes, the sequence of testing positions was consistent; starting with a supine position and progressing to sitting. However, the testing sequence in each testing position was randomised for each participant.[423] The movement to be tested was demonstrated to the participant, after which they were asked to perform the movement to confirm understanding and to ensure that stabilisations were adequate. Standard verbal encouragement was provided by the researcher

during each maximal contraction. Participants were instructed to avoid explosive contraction and to rather increase effort gradually over about two seconds to maximum once they heard the instruction “ready, GO”. Participants were instructed to then hold the maximum contraction for a further five seconds and cease contraction once the researcher gives the instruction to relax.[421,423] Two trials were completed for each muscle group, and the mean was used for final analysis. In the event that more than 10% difference was noted between the two trials, a third trial was performed, and the mean of the two best trials used. Testing was done bilaterally and strength values were averaged for the two sides. Results were recorded in Newton and rounded to one decimal. The HHD’s piston and force pad was always held perpendicular to the limb segment to which it was being applied to. The specific test position for each muscle group is provided as part of the data collection form in Appendix K.

7.7.7.4. Bone mineral density

Bone status was evaluated by means of calcaneal quantitative ultrasound (QUS), using the SONOST 3000 Ultrasound Bone Densitometer (OsteoSys, Korea). Compared to dual energy X-ray absorptiometry (DEXA), QUS is relatively inexpensive, radiation-free, and portable; and has been recently been confirmed as a useful screening tool for monitoring BMD in PLHIV.[424–427] Although its use in clinical practice remains an area of research and is device-specific, QUS offers an appropriate tool for comparing BMD between different groups and identifying factors associated with variation in BMD, especially in resource-limited settings where DEXA is not available.[426,428,429] The SONOST QUS device has been used in South African coloured, black and white populations.[429,430] The QUS device was calibrated once daily, prior to measurements, using a phantom object.[431] Measurements were conducted with the participant sitting comfortably facing the device and with the non-dominant foot[432–434] (calcaneus) placed on the support platform for measurement. Three re-positioned trials were conducted per foot to obtain an average measure. Bone status was expressed as the T-score (standard deviation from the mean in healthy young adults of the same gender), Z-score (standard deviation in persons of the same age and gender) and bone quality index (BQI), which is calculated by the QUS device from speed of sound (SOS in m/s – marker of bone density and elasticity) and broadband ultrasound attenuation (BUA in dB/MHz – indicator of bone structure[429]) and has a lower precision error than either of these variables alone.[431]

7.7.7.5. Level of physical activity

Engaging in physical activity for less than 60 minutes per week (or less than two days a week) was regarded as low physical activity, whilst engaging in mild to moderate exercise for more

than 60 minutes per week or participating in at least 30 minutes of moderate (or higher intensity) exercise for at least five days a week (or at least 150 minutes per week) were grouped together and considered as moderate-to-high levels of physical activity.[435] Participants who responded "none" to the question, were considered as participating in no exercise. For further analyses, participants were dichotomised into "low" (i.e. including "none") and moderate-to-high levels of physical activity.

7.7.7.6. Chronic pain and cognitive function

Information on chronic pain and cognitive function was recorded as part of the self-administered questionnaire (Appendix K) using, respectively, the bodily pain scale and the cognition scale from the HIV Medical Outcomes Survey (MOS-HIV). The MOS-HIV has been derived from the MOS-Short-Form-20[436,437] by adding constructs that are pertinent to PLHIV, including cognitive functioning, energy/fatigue, health distress, and quality of life.[437]

MOS-HIV subscales are scored on a scale ranging from 0 to 100, with higher scores indicating better perceived health. The reliability, construct validity, and responsiveness of the MOS-HIV scale and summary scores are widely reported and the instrument is one of the most widely used among those employed in studies of PLHIV.[409,436] The subscales of the MOS-HIV can be included as individual sections within a longer interview or questionnaire.[437]

Chronic pain was defined according to six levels of responses ranging from "none" to "very severe" to the question "How much bodily pain have you generally had during the past four weeks?" along with a five-level response ("Not at all" to "extremely") to the question "During the past four weeks, how much did pain interfere with your normal work (or your normal activities, including work outside the home and housework)?".[54] The four-week recall may be questioned as a true measure of chronic pain; however, at the time of study no validated chronic pain questionnaire was available for PLHIV in South Africa. Raw pain scores for both these questions were recoded as per MOS-HIV instructions so that a lower score represented a worse outcome,[437] and the raw recoded scores of individual items in the MOS-HIV pain domain were summed (resulting in a score range of two to 11). These raw scores were then transformed according to the instruction manual[437] (to obtain a score ranging from zero to 100, with a higher score indicating better functioning) using the equation:

$$pain_{transform} = 100 \div (11 - 2) \times (pain_{raw} - 2)$$

Cognitive functioning was assessed using the six-item HIV-MOS cognitive dimension, which measures the degree of cognitive difficulties that participants have experienced over the past four weeks. Participants were asked to indicate how much of the time they have had difficulty to reason or solve problems, been forgetful, had difficulty with paying attention and with concentrating on activities. Raw scores were summed to a maximum score of 24 and transformed to obtain a score out of 100 (no recoding was necessary since the lowest level already corresponded to the worst outcome):

$$cognitive_{transformed} = 100 \div (24 - 4) \times (cognitive_{raw} - 4)$$

The MOS-HIV cognitive domain measures functional status owing to neuropsychological impairment. Evidence supports the clinical utility of this brief self-report measure related to cognitive abilities in early HIV-1 infection for the screening of HIV-1-associated cognitive-motor disorders. The MOS-HIV cognitive domain has demonstrated significant associations with objective neuropsychological test performance overall and in specific domains, and seems particularly sensitive to changes in neuropsychological test performance (especially behaviours that involve neurocognitive or psychomotor speed) in early HIV-1.[438,439]

7.7.7.7. Substance use and HAART adherence

Alcohol and substance abuse information was based on self-report of current or prior abuse, according to quantity consumed per week[54] – these questions were contained in the EndoAfrica questionnaire. HAART adherence was based on self-reported categories: “prescribed HAART but refused”; “started HAART but now stopped”; “prescribed HAART but currently taking less than prescribed dose”; “started HAART but currently nonadherent”; or “started HAART and adherent”. PLHIV on HAART were deemed adherent if they indicated that they took their medication all or most of the time, i.e. missed no more than two doses per week (if on a twice-daily regimen) or no more than one dosage per week (if on a once-daily regimen.[440] Responses to the adherence questioning were afterwards dichotomised into “adherent” and “non-adherent”.[440]

7.7.7.8. Additional data extracted from the EndoAfrica study or its questionnaire

Sociodemographic and lifestyle data (age, gender, ethnicity/race, home language, educational level, employment status, monthly income, alcohol use over the past 12 months and current smoking status), medical history (polypharmacy, multimorbidity, hypertension, cardiovascular disease, diabetes, chronic fatigue, and chronic pulmonary disease) were extracted from the

EndoAfrica database, or recorded by the relevant research nurse/healthcare worker using selected pages from the EndoAfrica questionnaire (Appendix L). In addition, for PLHIV, the following were extracted: HIV duration in years, most recent CD4+ cell count, viral load (dichotomised as detectable or not), HAART history, including regimen and duration in weeks, C-reactive protein (CRP) levels in mg/L, haemoglobin (Hb) in g/dL, and creatinine in µmol/L. When these data were not available as part of the EndoAfrica dataset, the research nurse (Worcester) or the researcher (as registered physiotherapist) (Paarl) obtained the results (if available) confidentially from the relevant patient folder. Confidential access to medical folders were discussed and cleared with the clinic manager at the Paarl site; and was also included as part of the written informed consent provided by all participants.

7.7.8. Covariables

Although confounding was not considered in this study (in an effort to describe PLHIV in a way that they would "typically" present to clinicians), selected important covariables were considered which may feasibly influence locomotor performance in PLHIV. Increased BMI and the presence of peripheral neuropathy were controlled for as per exclusion criteria. Other covariables that could contribute to kinematic or clinical test outcomes were age (continuous data: years), gender (binary data: male/female), leg-length-normalised gait speed (continuous data: dimensionless) or leg length (continuous data: cm), anxio-depressive symptoms (binary data: defined as reporting problems on the EQ-5D-5L depression/anxiety domain, versus no problems), current smoking status (binary data: yes/no) and level of physical activity (binary data: none/low versus moderate-to-high).

Lower limb performance is known to be affected by advancing age in the general population as well as PLHIV,[154,287] and gender may influence kinematics in the coronal plane (due to biomechanical differences such as the larger quadriceps angle [Q-angle] in women) - although consistent correlations between gender and sagittal or transverse plane kinematics during gait are more controversial.[314,441] Leg length has been used as a surrogate measure for height[442] and both measures are often used to normalise gait speed and other temporal and spatial parameters in comparative biomechanical studies. Height and leg length both influence gait speed, with taller individuals usually walking faster than their shorter peers.[255] Co-morbid psychiatric disorders such as depression and anxiety have been suggested to have a detrimental effect on the degree of physical disability in PLHIV.[53] In the general population, depression-associated "sad walking" has been characterised by slowed gait speed, reduced

lower extremity joint ROM, and increased postural flexion.[443,444] Low physical activity has been associated with decreased gait speed[445] due to eventual loss of strength and aerobic capacity. Physical performance tests were adjusted for all listed covariables except gait speed, considering that gait speed forms an inherent part of some of the performance tests, and is a performance test itself.[32] COP data were adjusted for gender only (which may also serve as a proxy for foot size) and due to a lack of consistent evidence of relevant covariables to COP parameters. In the case of gait biomechanics, data were adjusted for leg-normalised gait speed, age and gender. Slower gait speed in patient groups relative to healthy groups is a major contributor to differences in gait angles and parameters, limiting characterisation of the potential gait pathophysiology.[245,446] Gait speed is reported to have a significant influence on joint/segment angles in the sagittal, coronal and transverse planes, as well as on TSPs.[447,448] Slower gait speeds generally impose decreased joint angle excursions and increased TSPs (particularly temporal or temporophasic parameters such as the stance and double support phases of the gait cycle) – although certain variables such as cadence, decreased ankle plantarflexion ROM and hip sagittal kinematics seem relatively robust to gait speed changes.[234,449] Sagittal knee joint kinematics and coupling motion of the knee joint and ankle plantarflexion, on the other hand, seem particularly susceptible to gait speed changes.[245] As a universal biologic phenomenon, reduced gait speed may serve as a proxy measure for various other conditions (for example depression, which may manifest via a slowed gait), and has been suggested as a reflection of the integrated performance of numerous organ systems as well as age-related changes.[450]

Additional potential covariables which did not significantly differ between PLHIV and SNP (such as pain) were not considered in statistical models.

7.8. Study procedures

Figure 7.6 outlines the data collection procedures. The entire data collection procedure lasted approximately 90 minutes per participant. This time included the collection of some additional data variables which are not reported in this dissertation, but will provide valuable information for additional analysis to be conducted at a later stage.

7.8.1. Preparation of the venue for gait and balance evaluation

The test venues in Worcester and Paarl were both private, well-lit rooms with sufficient space (minimum of about 10 metres of straight walking space) for gait analysis and clinical tests. The researcher obtained the keys for the respective venues on the day of testing and no other persons had unsupervised access to the venues on these days. A research assistant assisted

in setting up the test space. At both test sites, the rooms were equipped with air conditioning systems which were set at a comfortable room temperature. Masking tape was used to lay out a straight walkway for gait analysis (about eight metres, with one metre marked before and after). Within this course, a six-metre distance was marked for the six-metre walk tests; and two six-metre-long strips of masking tape were placed 20cm apart for the narrow walk component of the PPB. A standard-height (44.5 cm) chair was positioned against one of the walls for the chair rise tests.

The myoMOTION system was set up by placing the recording laptop and receiver module on a table positioned perpendicular to the gait walkway, and setting up a tripod web camera in front of the table and facing the walkway. The MatScan system was also connected to the laptop, and the pressure mat placed next to the walkway. The mat was always positioned in a similar orientation, perpendicular to the laptop station, so that participants' feet were orientated in the same direction with regards to the pressure mat. A black cross, printed full-size on an A4 sheet, was positioned against a wall at eye-level ahead of the pressure mat. A 30-cm wooden step was placed in an area of open floor space next to the walkway (facing the same direction as the walkway, i.e. parallel) and away from metal objects or electrical cable, to serve as a calibration station for the myoMOTION. Although the myoMOTION system does not require calibration of the test volume, participant calibration is required before and in-between trials. Participant calibration of the myoMOTION was described in detail in Section 4.10.2.

A quiet corner of the test venue was set up with a portable plinth for clinical evaluation of participants (joint ROM screening, muscle testing, QUS) as well as for questionnaire completion (a chair and table was provided). The QUS device was set up as per the manufacturer's instructions, with the power cable directly connected to the wall socket and the device at least 20cm away from the wall. At the start of each day of data collection, a once-off calibration of the QUS device was performed using a phantom object. Figure 7.5 shows the set-up of the myoMOTION system in the testing venues.

Figure 7.5. The set-up of the motion analysis systems in the test venues.

7.8.2. Questionnaire completion

All self-reported questionnaires were completed by the participant at the start of the testing session, prior to any other data collection procedures (i.e. before they became aware of their performance abilities), with either the researcher or a research assistant standing by for any questions.

The quality of self-reported data – as opposed to objective clinical or laboratory collected data – partly depends on setting an appropriate context for the study participant, ensuring that they are aware of the importance and relevance (within the context of the study) of their response.[437] This may elicit more appropriate responses from participants that more accurately reflect their self-perceived state.[437] Therefore, the following procedures were implemented during administration of the questionnaires:

- The relevant questionnaire was introduced and explained (including its purpose within the context of the study).
- The participant was alerted to the fact that the questionnaires contained no identifying particulars (e.g. name or ID number) except for an anonymous study code.
- Upon handing the questionnaire to the participant, it was paged through and explained how it was to be completed.
- The participant was allowed to ask questions prior to and during completion of the questionnaire.

- For a few participants, the questionnaires were administered by means of face-to-face interviews.[437] Since reading ability and comprehension vary among individuals, participants may vary in the extent to which self-completed responses to questionnaires are consistent and valid reflections of their subjective experience.[437] Participants who were functionally illiterate or had a reading ability below primary school level were thus provided with interview administration.[437]

7.8.3. Physical assessment

Following questionnaire completion and prior to further test procedures, height, weight and leg length were measured by the research assistant and screening of lower limb joint ROM as well as distal peripheral neuropathy was performed by the researcher, as previously described (measurement of joint widths was not necessary for the field study).

Sociodemographic information and medical history were recorded for each participant (Appendix L) by the research assistant, if not already done so by the research nurse. For EndoAfrica participants, these data were extracted from the overhead study, along with laboratory results confirming HIV status.

7.8.4. Participant preparation

Participants were orientated to the testing venue and the logistics of the subsequent testing procedures were explained. Each participant was scheduled for a single test visit and a maximum of four participants were tested per day. Participants were requested to wear shorts and a tight-fitting shirt (or no shirt, if male) so as to enable efficient placement of IMUs (appropriate clothing were provided if the participant did not have their own). Participants remained barefooted during physical evaluation and all subsequent motion analysis and clinical tests.

7.8.4.1. IMU placement

IMUs were placed on seven lower limb segments as described in Chapter 4, Section 4.11.3. Participants were instructed not to touch or move any of the IMUs, particularly after calibration of the system.

7.8.4.2. Practice trials

Participants were allowed practice trials prior to each physical performance test, as mentioned for each relevant test above. Prior to any of these, the dual task familiarisation (described in Section 7.7.4.5) was performed in a seated position.

Practice trials for 3DGA were performed after the IMUs were fixated to their various body segments, but before the myoMOTION was calibrated. As in the validation and reliability studies (Chapter 4), these trials were performed along the marked walkway to familiarise participants to the feeling of walking with the IMUs placed on them. Participants were explicitly instructed to walk “as normal as possible” once the IMUs were attached.

7.8.5. MyoMOTION model calibration

The myoMOTION system was calibrated by having the participant stand stationary in a neutral reference posture (N-pose) on a 30-cm wooden block. Refer to Chapter 4, Section 4.11.5.2 for a detailed description of the calibration procedure, including the standardised instructions. This procedure was proven to demonstrate good intra-rater repeatability in Phase II of the project (see Chapter 5). The system was calibrated before the first gait trial, and subsequently in-between each gait trial.

7.8.6. Clinical test performance

Clinical tests were performed according to standardised instructions and according to the procedures explained in the relevant sections above and Appendix H. The performance sequence was randomised by drawing cards with test allocation from a box (although the order of testing within the PPB was adhered to; i.e. the balance component, then the chair rise component, followed by the short walk tests). This methodology attempted to mitigate the effects of fatigue or learning on test performance.

7.8.7. Instrumented gait analysis

Participants started walking approximately one metre before the taped line on the floor and ended after crossing the second line. MyoMOTION recordings were manually started and stopped as soon as the participant crossed each of these lines, respectively. Each participant performed three recalibrated gait trials per gait condition, namely usual-paced, fast-paced and dual task. Gait trials immediately followed myoMOTION calibrations and the conditions

(condition and also task) were randomised to limit the effects of familiarisation and fatigue on gait, as well as balance, tasks. Participants walked barefoot for all trials.

For the gait recordings, participants were instructed to look ahead and walk comfortably in a straight line, and not to focus on the masking tape lines on the floor. Additionally, participants were instructed to perform each of the three subsequent trials per condition (usual-paced, fast-paced and dual task) as they did the previous trial (i.e. not to speed up as they become more familiar with the procedures). Participants were also requested to notify the researcher immediately should any of the IMUs become loose. For the fast-paced task, participants were instructed to walk as fast as they could without running, as if they were late for a departing bus or taxi.[451] For the dual task condition, participants were instructed to count backwards in the units determined during the seated practice trial (see Section 7.7.4.5) without prioritising either task. Refer to Appendix I for the specific instructions for each task condition.

A gait trial was deemed successful if the participant did not target any lines on the floor by looking down at it or by noticeably changing their stride length, and if the researcher noted three strides per limb. The intercepted gait trials were performed in alternating directions and after each trial, the participant performed a balance trial, where after they returned immediately to the wooden platform for the next pre-walk calibration.

7.8.8. Instrumented postural balance assessment

In addition to a verbal instruction, the SLS procedure to be performed on the pressure mat was demonstrated to each participant and one practice trial was permitted. Participants were instructed not to hop, shuffle or shift their feet relative to the mat surface, and to maintain the SLS position with arms crossed for as long and as still as possible, or until the verbal stop command was given. Data capture started with the foot-off event. The task was performed three times and up to a maximum of 30 seconds. Participants were allowed to choose a preferred stance leg.[392] The instructions for this test is provided in Appendix M.

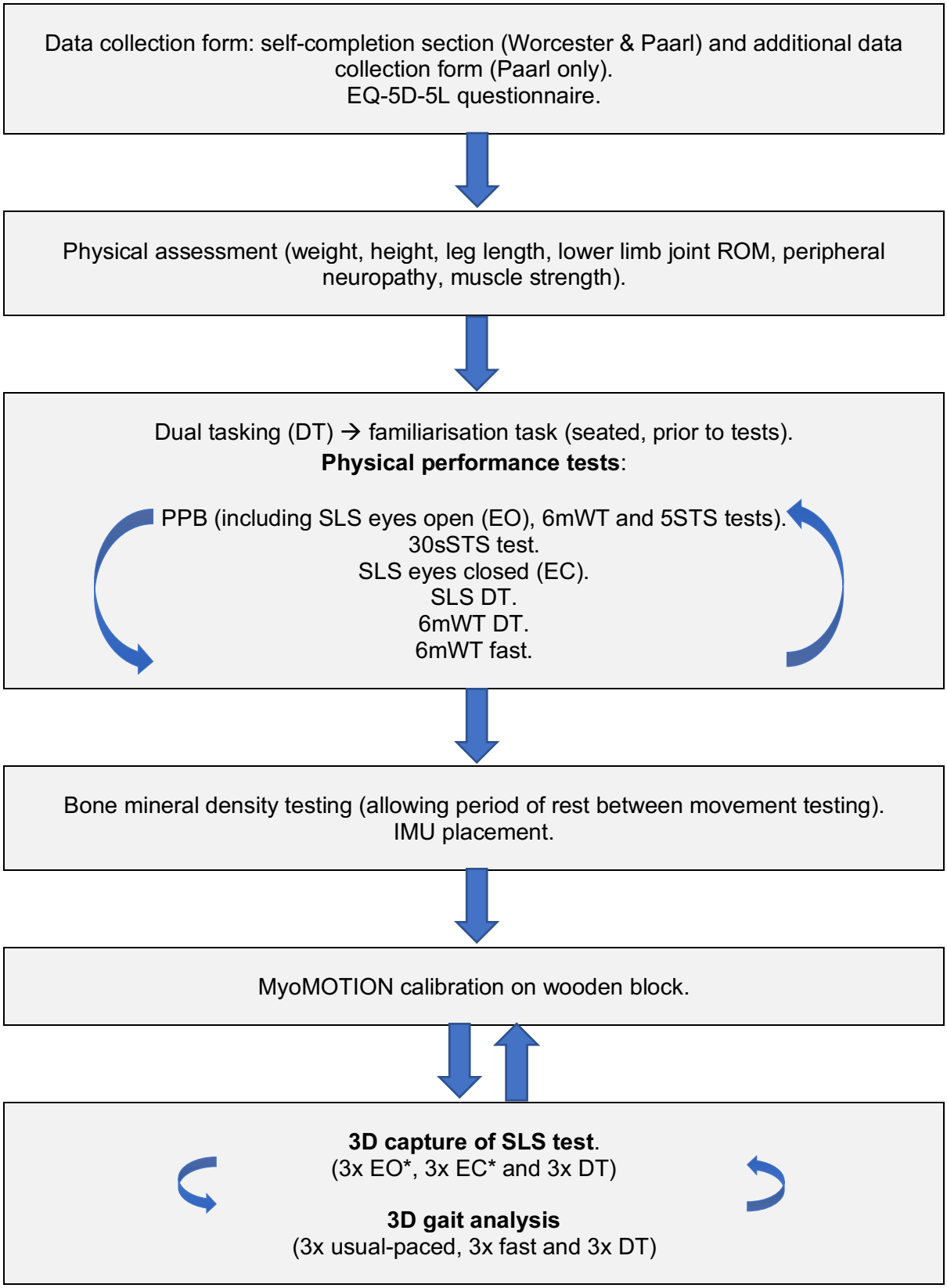

Figure 7.6. Schematic representation of the data collection procedures in the cross-sectional field study. Rounded arrows indicate that the individual tasks and conditions were executed in a random order for each participant.

7.9. Data reduction and processing

Performance test scores were calculated as previously explained in the relevant sections. Raw study data on the outcomes listed above were extracted and entered into a custom MS Office Excel spreadsheet. The MS Excel file was imported into SPSS as well as STATA for statistical analyses.

7.9.1. MyoMOTION

MyoMOTION and MatScan data processing was performed by a qualified neuromechanics laboratory analyst, in continuous close consultation with the PhD candidate. Gait data recorded by the myoMOTION and Noraxon's myoResearch (MR3) software were exported to single .csv files (for each trial). Data were then imported into MATLAB (2017a) for processing and analysis. The raw myoMOTION data were filtered using a 4th order zero-lag low pass Butterworth filter with a cut-off frequency of 6 Hz, to attenuate any noise within the signals. MyoMOTION data were not pre-processed, but were corrected for magnetic drift (distortion) post-recording on the foot, shank and thigh segments. Gait events were determined within the software (using a built-in algorithm). The cyclical gait events, defined by the foot contact and foot off events (and other custom key events), were then used to segment the data into gait cycles (starting and ending with subsequent foot contacts). Once the data were segmented, and prior to determining myoMOTION outcomes, the data were negated ("flipped") according the positive definitions of each joint/segment motion. The relevant TSPs and kinematic angular outcomes were then determined and the outcomes were subsequently exported to an Excel workbook, which was imported into the relevant statistical software.

7.9.2. MatScan

Raw COP data recorded by the MatScan were filtered using a 4th order Butterworth filter with a 10Hz cut-off frequency. These data were exported to MATLAB for processing and calculation of the relevant COP outcomes. Custom algorithms were developed according to definitions by Prieto et al.[378] for calculation of mean COP excursions and velocities for a task duration of 30 seconds. Given that participants' feet were aligned parallel to the pressure mat area with the same orientation for all participant throughout the study, the ML and AP directions of movement respectively were assumed as orthogonal and parallel to the MatScan area.

Invalid trials were considered those where foot shuffling or hopping occurred, or if the lifted leg touched down on the mat prior to 30 seconds. COP measurement outcomes suffer from error if shuffling of the feet (horisontal translation or rotation relative to the mat surface) occurs. The researcher therefore manually inspected plantar pressure videos (recorded by the MatScan software) of all participants to identify periods of foot shifting, or trials where the lifted foot touched down prior to 30 seconds. In the cases where such movements were noted, trials were discarded. For the remaining trials, the 30-second time periods containing the valid COP data, defined by start (foot off) and end (foot contact, or at 30 seconds) events, were analysed. Three attempts were allowed per task, and thus three recordings of the relevant task were available for each participant. The first successful trial for each participant was selected for processing. These data were exported from the MatScan software in the form of ASCII files.

7.9.3. The enhanced Gait Variability Index (EGVI)

EGVI calculations were based on the five specified TSPs, which were generated within MR3 software. Raw myoMOTION data were custom formatted by a motion laboratory technician for use within the MS Excel EGVI macro that was provided by the original author (A Gouelle) and EGVI calculations were performed in consultation with the author. For each participant, an EGVI score was calculated if a minimum of five absolute differences (at least 13 consecutive steps) were available. The raw data were obtained from the three short gait trials performed by each participant, and within each trial, a minimum of three consecutive values for each alternative parameter was required to enable EGVI calculation.[452] Gait variability is known to differ depending on whether data are collected from continuous walking or multiple short trials,[453] therefore the EGVI (which is designed to assess intra-trial variability) compensates for the inter-trial variability induced by such methodology by separating values obtained from different trials and standardising each using the mean of the series (leg and trial) to which it belongs.[375]

As a first step in EGVI calculation, and to compensate for inter-trial variability, ten (two values for each original raw TSP) alternative variables (p_n) need to be calculated for each lower limb. This was done as follows: the trial mean TSP_{ij} (for any given TSP "i" within any given trial "j") was ascribed a dimensionless value of 100%. For left and right legs separately, the within-trial TSP_{ij} foot falls were then expressed as percentages of the trial mean. Next, the differences in percentages between within-trial foot falls were determined over all trials. A mean and SD absolute difference of TSP_i foot falls was obtained in this manner, and provided the two

alternative parameters for each raw TSP (p_n). The mean represents the magnitude of the parameter's variability while the SD evaluates the consistency of the fluactuation.[375]

These alternative parameters were adjusted in relation to pre-specified weighting coefficients (c_n) determined by Gouelle et al.[375] through a principal component analysis. For each participant (α), the products were summed as:

$$s^{\alpha} = \sum_{1}^{10} (p_n \times c_n)$$

The distance between the sum score of a PLHIV (α), and those of the SNP was calculated, and +1 was added to the computed distance[372]:

$$d^{\alpha,SNP} = |s^{\alpha} - s^{SNP}| + 1$$

A raw index score was obtained by calculating the natural logarithm of this difference:

$$EGVI_{raw}^{\alpha} = \ln(d^{\alpha,SNP})$$

The z-score was calculated:

$$zEGVI_{raw}^{\alpha} = \frac{EGVI_{raw}^{\alpha} - mean(EGVI_{raw}^{SNP})}{SD(EGVI_{raw}^{SNP})}$$

The EGVI score is determined from the z-score as follows:

$$EGVI^{\alpha} = 100 - 10 \times zEGVI_{raw}^{\alpha}$$

Each limb is considered independently, and an overall EGVI score is provided as well as the mean of left and right limbs. The overall EGVI score was used in this study.

7.10. Statistical analysis

All data were entered into a custom-built MS Excel worksheet (master dataset for the cross-sectional field study), and exported to statistical software for analysis. All statistical analyses were performed using the IBM Statistical Package for Social Sciences (SPSS Statistics) for Macintosh, Version 25.0 (International Business Machines Corporation, Armonk, NY) and STATA Version 14.2 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP). All *p*-values were two-tailed and the statistical significance level

was set at α = 0.05. Normal distribution of data was assessed statistically using Shapiro-Wilk tests, and visually using histograms, box-and-whisker plots and Q-Q plots.

7.10.1. Descriptive statistics

Participant characteristics (demographic, anthropometric, lifestyle, medical and clinical), self-reported function, fall-related outcomes, clinical test performance as well as 3D gait and balance outcomes were summarised using mean and standard deviation (SD) for normally distributed continuous variables, median and interquartile range (IQR) for skewed continuous variables, and percentages for categorical outcomes. For physical performance tests and biomechanical data, the range was also described. Additionally, for physical performance tests with maximum and minimum cut-off scores, score distributions were examined for floor and ceiling effects. The percentage of participants respectively scoring the minimum (floor) and maximum (ceiling) possible scores were reported. Such effects indicate the limited ability of a clinical test to discriminate between participants due to the test either being too difficult or too easy.[454] Floor and ceiling effects >15% were deemed significant.[455]

7.10.2. Differences between people living with HIV-1-infection (PLHIV) and HIV-seronegative participants (SNP)

Differences in continuous data between PLHIV and SNP were determined by using parametric analysis (independent Student's t-tests) for normally distributed data and non-parametric analysis (Mann-Whitney U tests) for skewed data. Percentages between groups were compared using chi-squared tests or, in the case of small sample sizes, Fisher's exact tests. To illustrate absolute differences in the relevant measurement units (e.g. scores or degrees), mean differences or Hodges-Lehmann's median differences[456] and the respective 95% confidence intervals (CI) were calculated for clinical tests and biomechanical outcomes. The 95% CI for Hodges-Lehmann's median differences are robust to the possibility that the two population distributions differ in ways other than location, such as having unequal variances. Bonferroni correction for multiple comparisons were not made, given that the number of outcomes for comparison were defined a priori, and considering the correlated nature of many gait outcomes.[457] Comparisons were therefore assessed as planned at the 5% level of significance.

A second set of statistical analyses was conducted to compare physical performance tests and biomechanical data between PLHIV and SNP whilst statistically controlling for selected covariables. Candid covariables were selected based on their potential important influence on

the relevant outcomes as previously reported in the literature. For physical performance tests, covariables entered into the model included age (continuous data), gender (binary data), leg length (continuous data), depression/anxiety symptoms (binary data), current smoking status (binary data) and level of physical activity (binary data). For biomechanical gait outcomes, covariables included dimensionless gait speed (to also account for leg length differences), age and gender (gait speed was considered a proxy for the effects of smoking, depression and level of physical activity). For COP parameters, covariables included gender.

Based on the aim of describing between-group differences (as opposed to ascertaining risk prediction), factorial analyses of covariance (ANCOVA) were used to test for group differences while adjusting for the various covariables. HIV status constituted the independent variable and separate ANCOVA models were created for each dependent variable. Normality of the distribution of model residuals were confirmed for all dependent variables.[458] Treating clinical performance tests as continuous variables in all analyses,[459] for each dependent outcome (e.g. kinematic angle, test result, etc.) potential interactions between HIV-serostatus and the factors and covariables included in the ANCOVA were examined for significance. Where significant interactions were noted, an *HIV x covariable* term was included in the final model.[460] If any interaction term was not statistically significant, it was removed from the model and the analysis rerun without the interaction term.[460] Strictly speaking, this no longer constitutes a traditional ANCOVA; but still suffices as a linear model and is appropriate for observational (as opposed to experimental) designs. By including the interaction, the assumption of homogeneity of slopes is relaxed and therefore a universal assessment of the effect of HIV can no longer be made, as these differences depend on the value of the covariable. Although it is possible to describe the effect of HIV-serostatus at selected values of the covariable (e.g. at the quartiles) such analyses were beyond the scope of the research question of this study. Homogeneity of variance was confirmed by checking for a non-significant Levene's test ($p > 0.05$). In the case of a significant Levene's test, estimated parameters with robust heteroskedasticity-consistent (HC3) standard errors were calculated.[461]

7.10.3. Correlations between physical performance tests, EGVI, self-reported function and fall-related outcomes

Correlations (strength and direction of relationships) between ordinal physical performance test results and EGVI scores, self-reported function and fall number and history were evaluated using non-parametric Spearman's rank (r_s) correlation coefficients. Pearson product-moment (r) coefficients were calculated between normally distributed variables.

Correlations of 0.2 ≤ 0.39 were deemed weak; 0.4 ≤ 0.59 were considered moderate; 0.6 ≤ 0.79 were considered strong; and 0.8 ≤ 1.0 very strong.[462] Associations between the selected clinical tests and the binary variables (yes/no) of having experienced any fall over the past year, as well as having a fear of falling, were assessed using independent Student's t-test or Mann-Whitney U tests, depending on the data distribution.

PART III

CHAPTER 8

RESULTS: CROSS-SECTIONAL FIELD STUDY

8.1. Descriptive profile of the HIV-seropositive and HIV-seronegative groups

8.1.1. Sample composition

The study population consisted mainly of patients visiting primary health care clinics in Worcester and Paarl. Between May 2016 and December 2017, 186 potentially eligible participants were assessed by the research nurses or HIV-counsellors for eligibility (including counselling and rapid HIV screening for those with an unknown serostatus). One-hundred-and-six participants were confirmed eligible and participated in the study (PLHIV = 54 and SNP = 52).

The primary reasons for non-participation were unavailability for further testing following EndoAfrica[vii] participation (people living with HIV-1 infection [PLHIV], 7%), refusal (PLHIV, 14% and seronegative participants [SNP], 24%), participants not arriving for participation after being screened (PLHIV, 5% and SNP, 38%), having a body mass index (BMI) > 25kg/m^2 (PLHIV, 13% and SNP, 18%), and, amongst SNP, refusal to undergo HIV testing (SNP 18%). Other reasons for non-participation included active pulmonary tuberculosis (TB), age >65 years or feeling unwell (PLHIV, 7%) and alcohol intoxication (SNP, 3%).

Two SNP who passed the verbal screening were later found to have used alcohol on the morning of data collection. Their data sets were excluded from analysis in accordance with the study exclusion criteria. Due to technical failure of the myoMOTION system resulting in corrupted 3D data (not able to turn the virtual floor in MR3 software), data sets from the first four PLHIV were also excluded from analysis. Consecutive sampling continued until a final sample of 50 PLHIV and 50 SNP data sets were available for analysis.

[vii] *The overhead EndoAfrica study is described in Chapter 4, Section 4.7.*

The study protocol evolved during the early stages of data collection and subsequently bone mineral density (BMD) testing was only included from the thirteenth participant onwards (after the Stellenbosch University [SU] Health Research Ethics Committee [HREC] approved the protocol amendment); resulting in bone status data being available for n = 92 (92%) of participants (44 PLHIV and 48 SNP). Similarly, dual tasking was only introduced from the seventeenth participant, resulting in dual task data being available for n = 88 (88%) of participants (41 PLHIV and 47 SNP). Other reasons for missing data were inability to perform single leg stance (SLS) with eyes closed (EC) (n = 4 PLHIV) or during dual tasking (n = 2 PLHIV), missing laboratory results from patient folders (some non-EndoAfrica participants) and failure to fill in the EQ-5D-5L questionnaire correctly. Figure 8.1 illustrates the inclusion and exclusion process of study participants and their data.

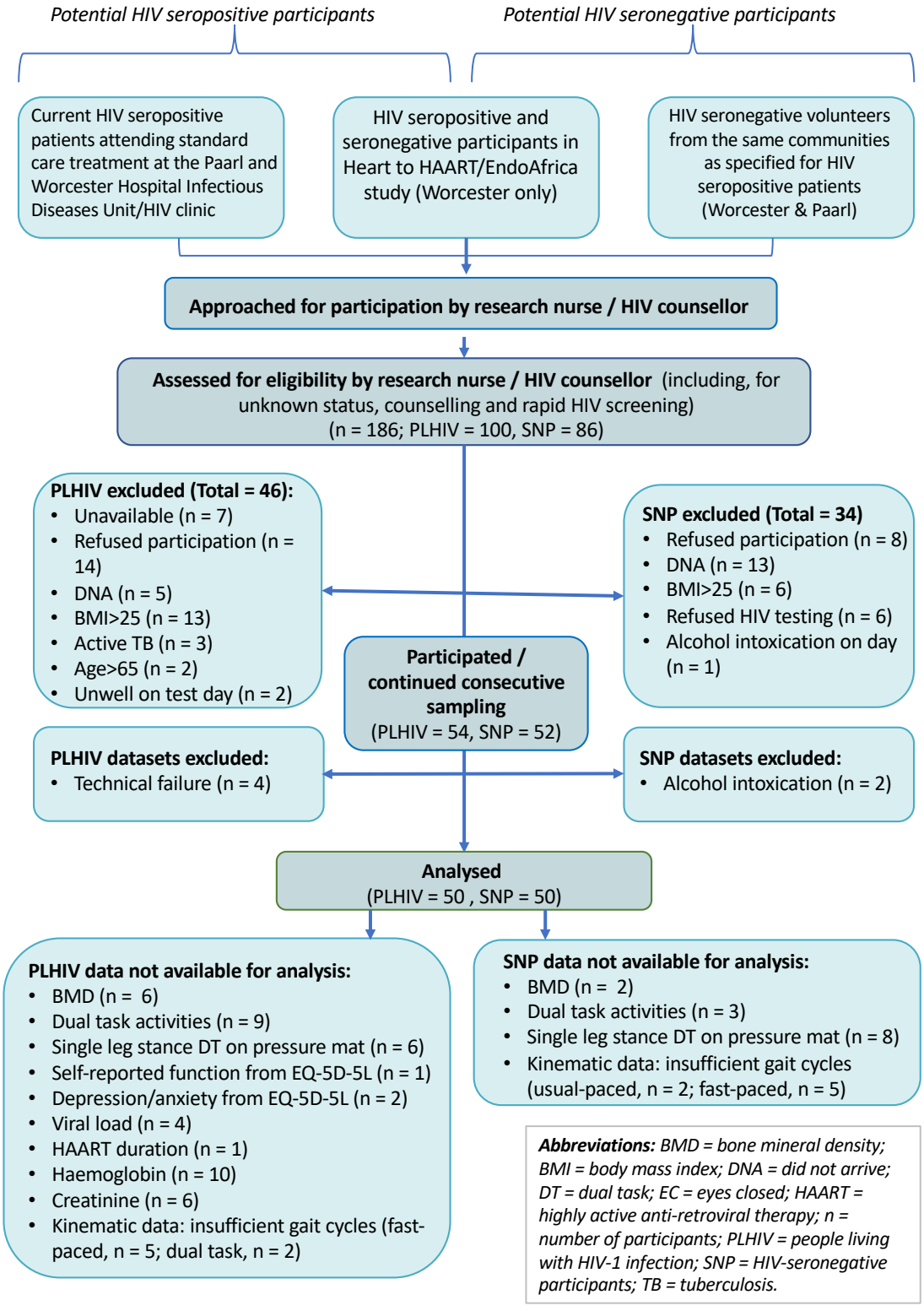

Figure 8.1. Flow diagram of participant and data inclusion and exclusion for the cross-sectional field study.

8.1.2. Sociodemographic characteristics

Sociodemographic characteristics of the participants in the PLHIV and SNP groups are presented in Table 8.1. Relative to SNP, PLHIV were 5.51 years older. Both groups had a higher distribution of younger versus older age groups. Both groups were predominantly female, but SNP included significantly more women than the PLHIV group. Ethnicity/race distribution differed significantly between groups, although both groups predominantly comprised of coloured participants. PLHIV were more likely to be employed (either part time or full time).

Table 8.1. Sociodemographic characteristics of PLHIV and SNP in the cross-sectional study.

Characteristics	PLHIV (n = 50)	SNP (n = 50)	*p*-value
Age (years)	36.61 (31.96; 45.59)	31.10 (23.22; 45.07)	**0.017**[§]
Age younger than 50 years	80%	86%	0.424[†]
Female gender	58%	80%	**0.017**[†]
Ethnicity/race			**0.012**[‡]
Coloured	84%	98%	
Black	14%	0%	
White	2%	2%	
Home language			**0.007**[‡]
Afrikaans	88%	94%	
English	0%	6%	
isiXhosa	12%	0%	
Education lower than Grade 12	58%	56%	0.840[†]
Employed	58%	40%	0.072[†]
Total household income per month			0.645[‡]
<R1,000 p/m	32%	24%	
R1,000 – R4,999	44%	48%	
R5,000 – R9,999	16%	14%	
R10,000 – R20,000	8%	10%	
>R20,000	0%	4%	

Abbreviations: n = number of participants; PLHIV = people living with HIV-1 infection; Q1 = first quartile; Q3 = third quartile; SNP = HIV-seronegative participants.
Data are presented as median (Q1; Q3) or percentage. [§] Mann Whitney U test; [†]Chi-square test of homogeneity; [‡]Fisher's exact test (r x 2). p-values in bold print indicate statistical significance at p < 0.05.

8.1.3. Anthropometrics and clinical measurements

PLHIV on average had longer leg lengths than SNP. Bone mineral density measures were significantly lower in PLHIV. Relative to SNP, the percentage of osteopaenia and osteoporosis cases in PLHIV was larger, although these differences did not reach statistical significance. Lower limb muscle testing revealed that PLHIV had significantly weaker maximum isometric knee extensor (mean difference of -14.73 Newton (N), p = 0.045) and knee flexor strength (mean difference of -14.06 N, p = 0.020) than SNP; no other investigated lower limb muscle groups demonstrated significant differences (Table 8.2).

Table 8.2. Clinical measurements and anthropometric characteristics of PLHIV and SNP in the cross-sectional study.

Characteristic	PLHIV (n = 50)	SNP (n = 50)	*p*-value
Height (m)	1.63 ± 0.09	1.60 ± 0.08	0.061[$]
BMI (kg/m^2)	21.49 ± 4.80	20.40 ± 4.95	0.677[$]
Leg length (cm)	86.84 ± 5.45	84.45 ± 4.12	**0.016[$]**
Bone status (based on T-score)[a,b] *n(PLHIV) = 44; n(SNP) = 48*			0.095[‡]
Osteopaenia	56.82%	41.67%	
Osteoporosis	4.55%	0.00%	
Normal	38.64%	58.33%	
T-score[#]	-1.15 (-1.43; -0.85)	-0.82 (-1.32; -0.10)	**0.016[§]**
Z-score[#]	-1.13 (-1.43; -0.67)	-0.73 (-1.27; -0.03)	**0.024[§]**
BQI	81.30 (77.05; 87.43)	88.70 (79.17;102.80)	**0.010[§]**
Muscle strength			
Plantarflexors (N)	169.16 ± 36.15	181.91 ± 30.28	0.059[$]
Dorsiflexors (N)	133.03 ± 23.94	131.81 ± 23.62	0.798[$]
Knee extensors (N)	189.10 ± 38.03	203.83 ± 34.34	**0.045[$]**
Knee flexors (N)	147.06 ± 32.57	161.12 ± 26.57	**0.020[$]**
Hip extensors (N)	216.87 ± 38.97	212.16 ± 34.25	0.523[$]
Hip flexors (N)	205.54 ± 37.28	193.78 ± 28.18	0.078[$]
Hip abductors (N)	103.64 (86.38; 126.36)	109.19 (100.14; 125.82)	0.082[§]

Abbreviations: BMI = body mass index; BQI = bone quality index; cm = centimetres; m = metres; n = number of participants; N = Newton; PLHIV = people living with HIV-1-infection; Q1 = first quartile; Q3 = third quartile; SD = standard deviation; SNP = HIV-seronegative participants.

Data are presented as mean ± SD or median (Q1; Q3). [$]Independent Student's t-test; [‡]Fisher's exact test (rx2); [§] Mann Whitney U test. p-values in bold print indicate statistical significance at p < 0.05.
[a]Bone mineral density data not collected for n = 6 PLHIV and n = 2 SNP, as QUS was only added to the study protocol after the first eight participants.

8.1.4. Lifestyle characteristics

Lifestyle characteristics (Table 8.3) were similar between PLHIV and SNP, except for level of physical activity and smoking status. Relative to SNP, PLHIV were less likely to be current smokers and more likely to report moderate to high levels of physical activity, while SNP were more likely to report low or no physical activity.

Table 8.3. Lifestyle characteristics of PLHIV and SNP in the cross-sectional study.

Characteristic	PLHIV (n = 50)	SNP (n= 50)	*p*-value
Physical activity			**0.033[†]**
None	12%	30%	
Low	44%	46%	
Moderate to high	44%	24%	
Alcohol use over past 12 months			0.334[‡]
None	48%	38%	
Light	36%	54%	
Moderate	12%	6%	
Heavy	4%	2%	
Current smoker	52%	72%	**0.039[†]**
Injection drug use, ever	2%	0%	0.500[†]

Abbreviations: n = number of participants; PLHIV = people living with HIV-1-infection; SNP = HIV-seronegative participants.
[†]Chi-square test of homogeneity; [‡]Fisher's exact test (r x 2). p-values in bold print indicate statistical significance at p < 0.05.

8.1.5. Medical history

PLHIV did not differ significantly from SNP regarding medical history (Table 8.4), with the exception of more PLHIV reporting symptoms of depression/anxiety, as measured by the relevant EQ-5D-5L domain and more PLHIV being subject to nonantiretroviral polypharmacy. The most common non-ART medications in descending order for PLHIV were vitamin supplements (especially Vitamin C), hypertension diuretics, ACE inhibitors, analgesics (antipyretics), beta-blockers, statins, calcium channel blockers, bronchodilators, aspirin, anti-inflammatories, analgesics (opioids) and tricyclic antidepressants. For SNP, the most common

medications in descending order were ACE inhibitors, hypertension diuretics, beta-blockers, corticosteroids, statins, aspirin, analgesics (opioids) and biguanides.

Table 8.4. Medical history in PLHIV and SNP in the cross-sectional study.

Characteristic	PLHIV (n = 50)	SNP (n = 50)	*p*-value
Nonantiretroviral polypharmacy (two or more non-HAART medications)	32%	10%	**<0.001**†
Multimorbidity (two or more comorbidities)	8%	4%	0.678‡
Hypertension	20%	14%	0.424†
Cardiovascular disease	2%	2%	1.000‡
Diabetes Type 1 or 2	0%	2%	1.000‡
Chronic fatigue	6%	0%	0.242‡
Chronic pulmonary disease	8%	6%	1.000‡
Depression/anxiety[a] *n(PLHIV) = 48; n(SNP) = 50*	25%	4%	**0.003**†
Current (acute) pain *n(PLHIV) = 49; n(SNP) = 50*	34.7%	18%	0.059†
Chronic pain (MOS-HIV score)	77.78 (55.56; 88.89)	88.89 (77.78; 100.00)	0.127§
Cognitive function, (MOS-HIV score)	80.00 (60.00; 95.00)	87.50 (75.00; 95.00)	0.076§

Abbreviations: ART = antiretroviral therapy; n = number of participants; PLHIV, people living with HIV-1 infection; Q1 = first quartile; Q3 = third quartile; SNP = HIV-seronegative participants. Results presented as percentage or median (Q1; Q3). †*Chi-square test;* §*Mann Whitney U test;* ‡*Fisher's exact test. p-values in bold print indicate statistical significance at p < 0.05.*
[a]*Depression/anxiety: missing data for n = 2 PLHIV - one participant omitted the anxiety/depression question; another filled out the entire questionnaire (all domains) incorrectly.*
[b]*Current pain: missing data for n = 1 PLHIV who filled out the entire EQ-5D-5L questionnaire wrong.*

8.2. HIV-related characteristics

Table 8.5 presents disease-related characteristics of PLHIV. Most PLHIV (44%) had an HIV duration of five to 15 years. The average CD4+ count was below 500 cells/μL and less than half of PLHIV had undetectable viral loads. Almost all PLHIV (90%) were using HAART, with a median duration of about 2.3 years. The most common current HAART regimen was NNRTI-based (efavirenz/emtricitabine/tenofovir, n = 80%). Non-adherence (defined as missing more than two prescribed HAART dosages per week) was reported by 22.22% of HAART-users. Investigated laboratory results mostly fell within normal ranges reported for the general

population, although 48% of PLHIV had C-reactive protein (CRP) levels exceeding 3mg/L (normal value in the general population <3 mg/dL).

Table 8.5. HIV-related characteristics in the cross-sectional study (n = 50).

Variable	Estimate
Time since HIV diagnosis (years)	
<2 years	18%
2 – 5 years	32%
5<15 years	44%
>15 years	6%
Current $CD4^+$ T-cell count (cells/μL)	448.78 ± 232.99
Detectable HIV-1 RNA (≥50 cp/mL) *n = 46*[a]	54.30%
On HAART	90%
On first line HAART	84.44%
On second line HAART	15.56%
HAART duration (weeks) *n = 44*[b]	119 (62; 312)
Current HAART regime	
PI-based	20%
NNRTI-based	80%
INI-based	0%
NRTI in the regimen:	
None	2.22%
3TC only	2.22%
TDF only	2.22%
ABC/AZT + 3TC	13.33%
TDF + FTC	80%
HAART adherent	77.78%
CRP (mg/L) *n = 33*[c]	3.60 (1.45; 13.45)
Haemoglobin (g/dL) *n = 40*[c]	14.01 ± 1.90
Creatinine (μmol/L) *n = 44*[c]	64.50 (54.00; 72.00)

Abbreviations: 3TC = lamivudine/epivir; ABC = abacavir; AZT = azidothymidine/zidovudine/retrovir; cells/μL = cells per microlitre; cp/mL = copies per millilitre; FTC = emtricitabine; g/dL = grams per decilitre; HAART = highly active antiretroviral therapy; HIV-1 RNA = viral load; INI = integrase inhibitor; mg/L = milligrams per litre; n = number of participants; NNRTI = non-nucleoside reverse-transcriptase inhibitor; NRTI = nucleoside reverse-transcriptase inhibitors; PI = protease inhibitor; PLHIV = people living with HIV-1 infection; Q1 = first quartile' Q3 = third quartile; SD = standard deviation; SNP = seronegative participants; TDF = tenofovir; μmol/L = micromole per litre.

Data are mean ± SD, median (Q1; Q3) or percentage.
[a]Viral loads missing for n = 4 participants who were not enrolled in the EndoAfrica (EA) study and had no values recorded in clinic folders.
[b]ART duration unknown for n = 1 participant as these data were not recorded in the clinic folder and the participant also did not know the duration.
[c]Laboratory results were obtained from the EA database for shared participants (n = 33); all other values were as the most recent results from clinic folders or coded as missing (n = 10 for Haemoglobin and n=6 for Creatinine) if not reported in folder.

8.3. Differences in self-reported function and fall history

8.3.1. Self-reported function

Self-reported function (Figure 8.2) was assessed in terms of three function-related domains from the EQ-5D-5L descriptive system. Responses to each of these domains were captured on a five-point Likert scale ("no problems" to "unable") and were then dichotomised into "problems" and "no problems".[414] Relative to SNP, a significantly larger percentage of PLHIV reported problems with mobility (walking) (22.4% versus 8%, $p = 0.046$) and self-care activities (washing and dressing) (12.2% versus 2%, $p = 0.047$), while the percentage of PLHIV reporting problems with usual activities (e.g. work, study, housework, family or leisure activities) did not differ significantly from SNP (20.4% versus 8%, $p = 0.077$). Data were missing for one PLHIV who completed the entire questionnaire incorrectly, affecting all three domains.

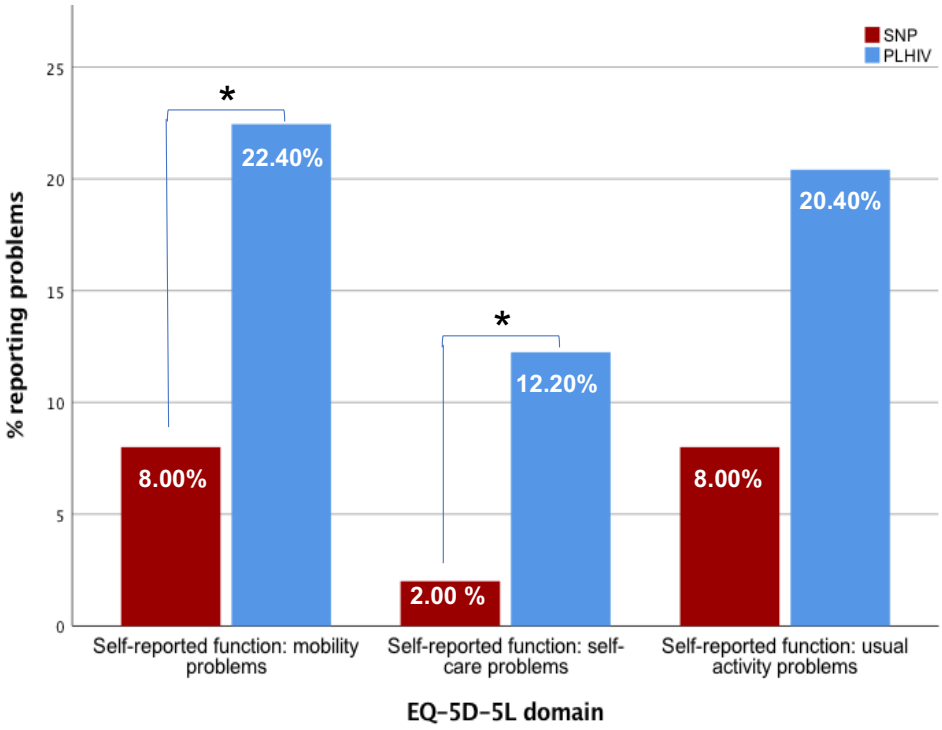

Figure 8.2. Self-reported function in PLHIV (blue) and SNP (dark red), reported in terms of three function-related domains from the EQ-5D-5L descriptive system. The asterisks indicate the domains that differed significantly (p < 0.05).

8.3.2. Falls and fear of falling

The percentage of PLHIV who experienced any number of falls during the previous 12 months was significantly higher compared to SNP. The most common reasons reported for falling were accidentally tripping over objects (SNP and PLHIV) or legs giving way for no apparent reason (PLHIV). No significant differences were evident regarding the actual number of falls experienced, although trends were higher in PLHIV. More PLHIV reported having a fear of falling, although the difference was not statistically significant (Table 8.6).

Table 8.6. Fall history in PLHIV and SNP in the cross-sectional study.

Fall history	PLHIV (n = 50)	SNP (n= 50)	*p*-value
Any fall during the past 12 months	34%	16%	**0.038**†
Number of falls during the past 12 months			0.114†
Single fall	20%	10%	
Recurrent falls (two or more)	14%	6%	
Fear of falling	20%	14%	0.425†

Abbreviations: PLHIV = people living with HIV-1 infection; SNP = seronegative participants.
†Chi-square test of homogeneity. Bold print indicates values of statistical significance ($p < 0.05$).

8.4. Differences in clinical functional test performance

8.4.1. Health ABC Physical Performance Battery (PPB)

Unadjusted comparisons of the Health ABC Physical Performance Battery (PPB) (Table 8.7) revealed significantly lower scores (worse performance) for PLHIV versus SNP on total score as well as for all but the static balance test components. Minimum clinically important differences (MCID) for the PPB (total score) have been suggested as 0.12 points (small difference) to 0.22 points (substantial difference) across various conditions[385]; according to these criteria (albeit established in non-HIV populations), the difference in total PPB score (0.37 points) may correspond to a substantial clinically meaningful difference between PLHIV and SNP.

After controlling for age, gender, leg length, depression/anxiety symptoms, current smoking status and level of physical activity, the significant between-group differences remained for total-, gait- and chair rise scores. Adjusted analyses also revealed significant interactions between HIV-serostatus and depression/anxiety symptoms for both of the gait speed sub

scores (F = 6.16, p = 0.015 and F= 4.91, p = 0.029 for the usual and narrow tests, respectively), indicating that the effect of HIV-1 infection on gait speed scores depended on the presence or absence of depressive symptoms. These interactions are illustrated in Figure 8.3.

The PPB and its components demonstrated no floor or ceiling effects in either group, except for the balance score domain (highest level assessed = 30 seconds single leg stance [SLS] with eyes open): 70% of PLHIV and 90% of SNP respectively reached ceiling effects in this test component.

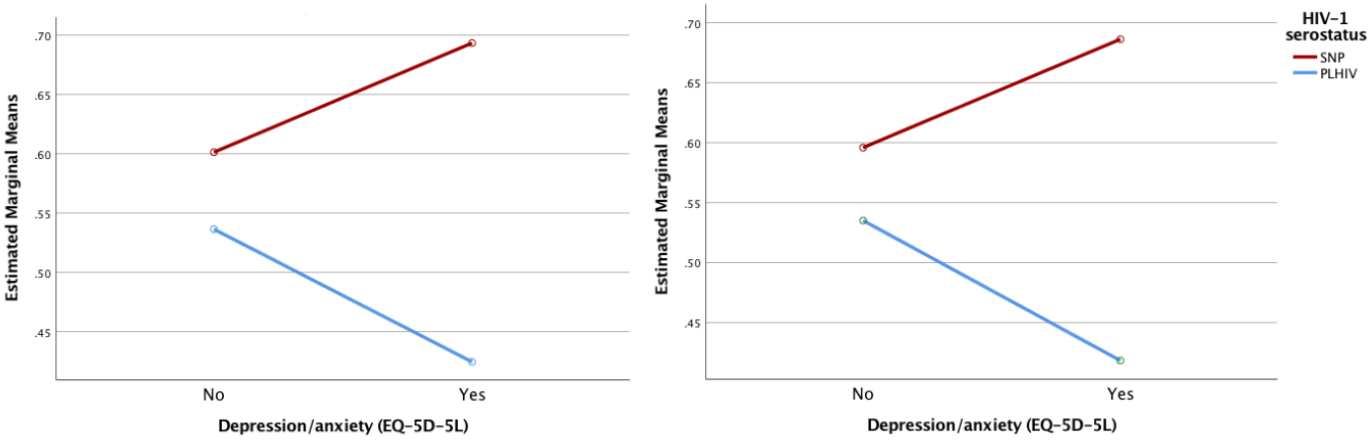

Figure 8.3. Profile plots demonstrating the interaction between HIV-serostatus and the presence or absence of depressive symptoms on gait speed scores. The left plot represents the usual six-metre gait sub score, and the right plot the narrow gait sub score. For both tests, the presence of HIV has a larger detrimental effect in the presence of depressive/anxiety symptoms.

Table 8.7. Health ABC Physical Performance Battery (PPB) performance in PLHIV and SNP. Blue arrows indicate the directional trend of the difference in PLHIV relative to SNP.

Clinical test components	Unadjusted				Adjusted			
	Estimate [% floor / % ceiling]		Mean or median difference (95% CI)	*p*-value	Mean ± SE (95% CI)		Mean difference ± SE (95% CI)	*p*-value
	PLHIV (n = 50)	SNP (n= 50)			PLHIV (n = 50)	SNP (n= 50)		
Health ABC Physical Performance Battery (PPB): score range 0 – 4								
PPB total score (median [IQR] [range])	2.44 (0.51) (1.25; 3.01) [0%; 0%]	2.78 (0.29) (2.20; 3.32) [0%, 0%]	-0.37 (-0.47; -0.24)	**<0.001**↓	2.36 ± 0.06 (2.25; 2.472)	2.67 ± 0.07 (2.53; 2.82)	-0.32 ± 0.09 (-0.48; -0.15)	**<0.001**↓
PPB balance score (median [IQR] [range])	1.0 (0.004) (-0.25; 1.00) [0%; 76%]	1.0 (0.0) (0.76; 1.00) [0%; 90%]	0.00 (0.00; 0.00)	0.057=	0.95 ± 0.02 (0.91 ± 0.99)	0.98 ±0.04 (0.90; 1.06)	-0.95 ± 0.50 (-1.94; 0.04)	0.060↓
PPB usual gait speed score (mean ± SD [range])	0.51 ± 0.12 (0.24; 0.76) [0%; 0%]	0.61 ± 0.09 (0.41; 0.81) [0%; 0%]	-0.10 ± 0.02[b] (-1.14; -0.06)	**<0.001**↓	0.52 ± 0.02 (0.49; 0.55)	0.61 ± 0.02 (0.58; 0.65)	-0.09 ± 0.02 (-0.14; -0.05)	**<0.001**↓

PPB narrow walk gait speed score (mean ± SD [range])	0.50 ± 0.14 (0.22; 0.75) [0%; 0%]	0.60 ± 0.11 (0.41; 0.94) [0%; 0%]	-0.10 ± 0.03[b] (-0.15; -0.05)	**<0.001**↓	0.48 ± 0.02 (0.44; 0.52)	0.64 ± 0.04 (0.55; 0.73)	-0.16 ± 0.47 (-0.26; -0.07)	**0.001**↓
PPB chair rise score (mean ± SD [range])	0.46 ± 0.12 (0.28; 0.75) [0%; 0%]	0.60 ± 0.15 (0.41; 1.00) [0%; 2%]	-0.14 ± 0.02[b] (-0.19; -0.10)	**<0.001**↓	0.46 ± 0.02 (0.42; 0.50)	0.55 ± 0.03 (0.50; 0.60)	-0.09 ± 0.03 (-0.14; -0.04)	**<0.001**↓

Abbreviations: CI = confidence interval; IQR = interquartile range; n = number of participants; PLHIV = people living with HIV-1 infection; PPB = Health ABC Physical Performance Battery; SD= standard deviation; SE = standard error; SNP = seronegative participants.
Covariables included age, gender, leg length, depression/anxiety symptoms, current smoking status and level of physical activity.
Unadjusted p-values were obtained via Mann-Whitney U tests or independent sample t-tests. Adjusted p-values were obtained via F-test in General Linear Model (ANCOVA).

8.4.2. Single leg stance tests (eyes closed and dual task)

Since SLS with EO (SLS EO) did not differ between groups as part of the PPB sub score, and given the high ceiling effects observed, this test was not analysed further as a lone-standing measure of clinical function performance. The SLS test was however assessed under two more challenging conditions, namely SLS with eyes closed (SLS EC), and SLS whilst performing a dual task (SLS DT). (Table 8.8) presents the unadjusted and adjusted results for these tests, assessed in terms of maximum time held in seconds (limit of 30 seconds).

Inspection of minimum and maximum scores showed that for the SLS EC test, 12% of PLHIV and 30% of SNP respectively reached a ceiling effect. In addition, 12% of PLHIV showed a floor effect (i.e. unable to hold the stance for at least one second[463]). SLS DT had high ceiling effects in both groups (63.4% and 91.4% in PLHIV and SNP respectively) – showing that most PLHIV, and almost all SNP, were able to perform the test up to the maximum time of 30 seconds.

For unadjusted analyses, Mann-Whitney U tests were run to determine if there were differences in SLS EC and SLS DT outcomes (maximum time held) between PLHIV and SNP. For both SLS EC and SLS DT, distributions of the maximum time held for PLHIV and SNP were not similar ($p < 0.001$). The median difference in maximum time held was significant for the eyes-closed condition (shorter time in PLHIV) but not for the dual task condition, as indicated by the 95% confidence intervals (CIs). After adjustment, PLHIV still had a significantly lower adjusted mean SLS EC time compared to SNP. Adjustment for covariables rendered between-group differences in SLS DT insignificant.

Table 8.8. Single leg stance (SLS) test performance in PLHIV and SNP. Blue arrows indicate the directional trend of the difference in PLHIV relative to SNP.

Clinical test components	Unadjusted				Adjusted			
	Median (IQR) (range) [% floor; % ceiling]		Median difference (95% CI)	*p*-value	Mean ± SE (95% CI)		Mean difference ± SE (95% CI)	*p*-value
	PLHIV	SNP			PLHIV	SNP		
Single leg stance (SLS) test (maximum time 30 sec)								
Eyes closed, seconds	7.93 (9.70) (0.00; 30.00) [12%; 12%]	15.04 (20.78) (4.00; 30.00) [0%; 30%]	-6.13 (3.00; 10.46)	**<0.001**↓	11.27 ± 1.55 (8.19; 14.35)	17.30 ± 1.94 (13.45; 21.14)	-6.02 ± 1.96 (-9.92; -2.13)	**0.003**↓
Dual task, seconds *n(PLHIV) = 41; n(SNP) = 47*[a]	30.00 (9.85) (2.00; 30.00) [0%; 63%]	30.00 (0.00) (11.92; 30.00) [0%; 92%]	0.00 (0.00; 0.00)	**0.002*** =	24.39 ± 1.35 (21.72; 27.07)	29.11 ± 1.59 (25.95; 32.27)	-4.72 ± 2.54 (-9.79; 0.35)	0.063↓

Abbreviations: CI = confidence interval; IQR = interquartile range; PLHIV = people living with HIV-1 infection; SE = standard error; SNP = seronegative participants.

Covariables included age, gender, leg length, depression/anxiety symptoms, current smoking status and level of physical activity.

** indicates a Mann-Whitney U p-value that represents a difference in score distributions between groups, as opposed to a difference in medians – the reader is advised to refer to the median difference and 95% CI for a more clinically relevant interpretation..*

[a]*Dual task (DT) activities were only included later in data collection protocol; thus no DT data were collected for n (SNP) = 3 and n (PLHIV) = 9.*

8.4.3. Six-metre gait speed test (usual-paced and dual task)

Gait speed over six metres (Table 8.9) was significantly slower in PLHIV relative to SNP in both task conditions but more so under the more challenging circumstance of performing a dual task. Mean ± SE differences between PLHIV and SNP were -0.20 ± 0.04 (95% CI = -0.29 m/s to 0.12 m/s) for the usual-paced condition and -0.25 m/s ± 0.05 (95% CI = -0.36 m/s to 0.15 m/s) for the dual task condition. For both tasks the differences between PLHIV and SNP exceed the MCID of 0.1 m/s generally reported across various populations for gait speed.[464] After adjustment, the mean difference remained larger than 0.1 m/s and significant ($p < 0.001$) for both usual-paced and dual task gait. Adjusted analysis showed a statistically significant interaction between HIV-serostatus and depression/anxiety on usual-paced (but not dual task) gait speed over a six-metre course ($F = 5.48$, $p = 0.021$). This interaction showed a similar pattern to what was observed for the gait speed sub scores of the PPB as was presented previously in Figure 8.3.

8.4.4. Chair rise tests

Table 8.10 presents the results for chair rise performance in PLHIV relative to SNP. Unadjusted comparisons revealed that PLHIV performed the Five-Times Sit-To-Stand (5STS) Test significantly slower (longer time required) than SNP (mean ± SE difference = -2.99 seconds, 95% CI = 2.07 seconds to 3.90 seconds, $p < 0.001$); exceeding the MCID of ~2 seconds reported for this test in various other populations[401] and suggested in PLHIV.[3] The difference was just under two seconds after adjustment and remained significant ($p < 0.001$). Adjusted analysis revealed a statistically significant interaction between HIV-serostatus and age on the time it took to complete five repeated chair rises ($F = 6.06$, $p = 0.016$). The interaction is depicted in Figure 8.4.

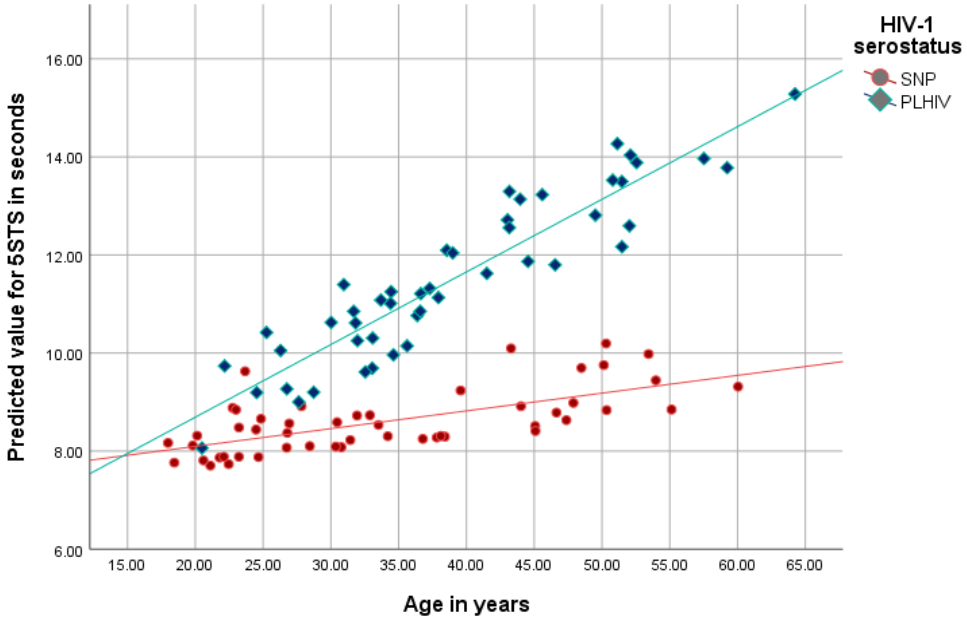

Figure 8.4. Grouped scatter plot demonstrating the interaction effect between HIV-serostatus and age on Five-Times Sit-To-Stand time, showing that the detrimental effect of HIV-serostatus increases with age.

Unadjusted comparisons for the 30-second STS (30sSTS) test revealed that PLHIV performed an average of 3.72 less repetitions than SNP ($p < 0.001$), exceeding the MCID of 2 to 2.60 repetitions previously applied in an HIV population.[402] After adjustment, simple main effects for HIV-serostatus demonstrated a significant mean difference of -4.81 repetitions ± 1.91 repetitions ($p = 0.013$).

Table 8.9. Six-metre Walk Test (6mWT) performance in PLHIV and SNP. Blue arrows indicate the directional trend of the difference in PLHIV relative to SNP.

Clinical test	Unadjusted				Adjusted			
	Mean ± SD (range)		Mean difference (95% CI)	*p*-value	Mean ± SE (95% CI)		Mean difference ± SE (95% CI)	*p*-value
	PLHIV (n = 50)	SNP (n= 50)			PLHIV (n = 50)	SNP (n= 50)		
Six-metre Walk Tests (6mWT) (speed in m/s)								
Usual-paced, m/s	0.99 ± 0.24 (0.47; 1.51)	1.22 ± 0.18 (0.81; 1.62)	-0.20 ± 0.04 (-0.29; 0.12)	**<0.001**↓	0.97 ± 0.04 (0.89; 1.04)	1.30 ± 0.08 (1.14; 1.45)	-0.33 ± 0.08 (-0.50; -0.17)	**<0.001**↓
Dual task, m/s *n(PLHIV) = 41; n(SNP) = 47*[a]	0.75 ± 0.27 (0.12; 1.21)	1.00 ± 0.23 (0.50; 1.76)	-0.25 ± 0.05 (-0.36; 0.15)	**<0.001**↓	0.74 ± 0.05 (0.65; 0.84)	0.96 ± 0.06 (0.84; 1.069)	-0.22 ± 0.06 (-0.33; -0.10)	**0.001**↓

Abbreviations: CI = confidence interval; m/s = metres per second; n = number of participants; PLHIV = people living with HIV-1 infection; SE = standard error; SNP = seronegative participants.

Covariables included age, gender, leg length, depression/anxiety symptoms, current smoking status and level of physical activity.

Unadjusted p-values were obtained via independent sample t-tests. Adjusted p-values were obtained via F-test in General Linear Model (ANCOVA). Bold print indicates statistical significance at p < 0.05.

[a]*Dual task (DT) activities were only included later in data collection protocol; thus, no DT data were collected for n (SNP) = 3 and n (PLHIV) = 9.*

Table 8.10. Chair rise test performance in PLHIV and SNP. Blue arrows indicate the directional trend of the difference in PLHIV relative to SNP.

Clinical test	Unadjusted				Adjusted			
	Mean ± SD (range)		Mean difference (95% CI)	*p*-value	Mean ± SE (95% CI)		Mean difference ± SE (95% CI)	*p*-value
	PLHIV (n = 50)	SNP (n= 50)			PLHIV (n = 50)	SNP (n= 50)		
Chair rise tests								
5STS, seconds	11.59 ± 2.83 (6.70; 18.00)	8.60 ± 1.63 (5.00; 12.23)	2.99 ± 0.46[a] (2.07; 3.90)	**<0.001**↑	11.45 ± 0.38 (10.69; 12.21)	9.53 ± 0.48 (8.58; 10.47)	1.92 ± 0.47 (0.99; 2.85)	**<0.001**↑
30sSTS, repetitions	15.94 ± 5.01 (8; 30)	19.66 ± 4.94 (11; 32)	-3.72 ± 0.99[a] (-5.59; -1.75)	**<0.001**↓	16.19 ± 0.86 (14.49; 17.89)	21.00 ± 1.78 (17.47; 24.53)	-4.81 ± 1.91 (-8.60; -1.02)	**0.013**↓

Abbreviations: 30sSTS = 30-second Sit-To-Stand Test; 5STS = 5-Times Sit-To-Stand Test; CI = confidence interval; n = number of participants; PLHIV = people living with HIV-1 infection; SE = standard error; SNP = seronegative participants.
Covariables in the adjusted model were age, gender, leg length, depression/anxiety symptoms, current smoking status and level of physical activity. Unadjusted p-values were obtained via independent sample t-tests. Adjusted p-values were obtained via F-test in General Linear Model (ANCOVA). Bold print indicates statistical significance at p < 0.05.[465]

8.5. Differences in biomechanical gait outcomes

As shown in Figure 8.1, selected participant datasets were excluded from kinematic outcomes due to not having enough valid gait cycles available (i.e. at least six cycles). Specifically, n = 2 SNP datasets (4%) were excluded from the usual-paced outcomes, n = 5 SNP (10%) and n = 5 PLHIV (10%) datasets were excluded from the fast outcomes, and n = 2 PLHIV trials (n = 4) were excluded from the dual task outcomes.

8.5.1. Temporal, spatial, temporophasic and temporospatial parameters (TSPs)

8.5.1.1. Usual-paced gait

Full data for unadjusted and adjusted TSP comparisons for usual-paced gait are presented in Table 8.11. Unadjusted comparisons demonstrated that at a usual pace, all TSPs differed significantly between PLHIV and SNP, except single support time as percentage of the gait cycle. The usual-paced gait speed of PLHIV was significantly slower than that of SNP. The slower speed in PLHIV resulted from both a shorter mean step length (resulting in a shorter mean stride length) and a lower mean cadence. The trends and significance of the differences for all said outcomes remained similar once normalised to leg length. PLHIV spent a longer percentage of the gait cycle in stance and double support. In accordance, PLHIV also demonstrated a shorter single support time, although this difference did not reach statistical significance.

After adjusting for age, gender and normalised gait speed, only stance time, step time, gait speed[viii] and normalised gait speed[ix] remained significantly different between groups. The direction of the differences remained the same. Relative to SNP, PLHIV thus demonstrated a slower gait speed with an increased stance and step time. However, HIV-serostatus only demonstrated a significant main effect for gait speed ($F = 15.79$, $p < 0.001$) and normalised gait speed ($F = 16.59$, $p < 0.001$). For stance and step time, significant interactions were noted between HIV-serostatus and gender ($F = 4.93$, $p = 0.29$ and $F = 4.95$, $p = 0.29$ for stance and step time respectively), as well as HIV-serostatus and speed ($F = 14.87$, $p < 0.001$ and $F =$

[viii] *Gait speed was only adjusted for age and gender.*

[ix] *Normalised gait speed was only adjusted for age and gender.*

12.33, p = 0.001 for stance and step time respectively). The effect of HIV on these outcomes thus depended on the gender of the participant. Figure 8.5 demonstrates these interactions.

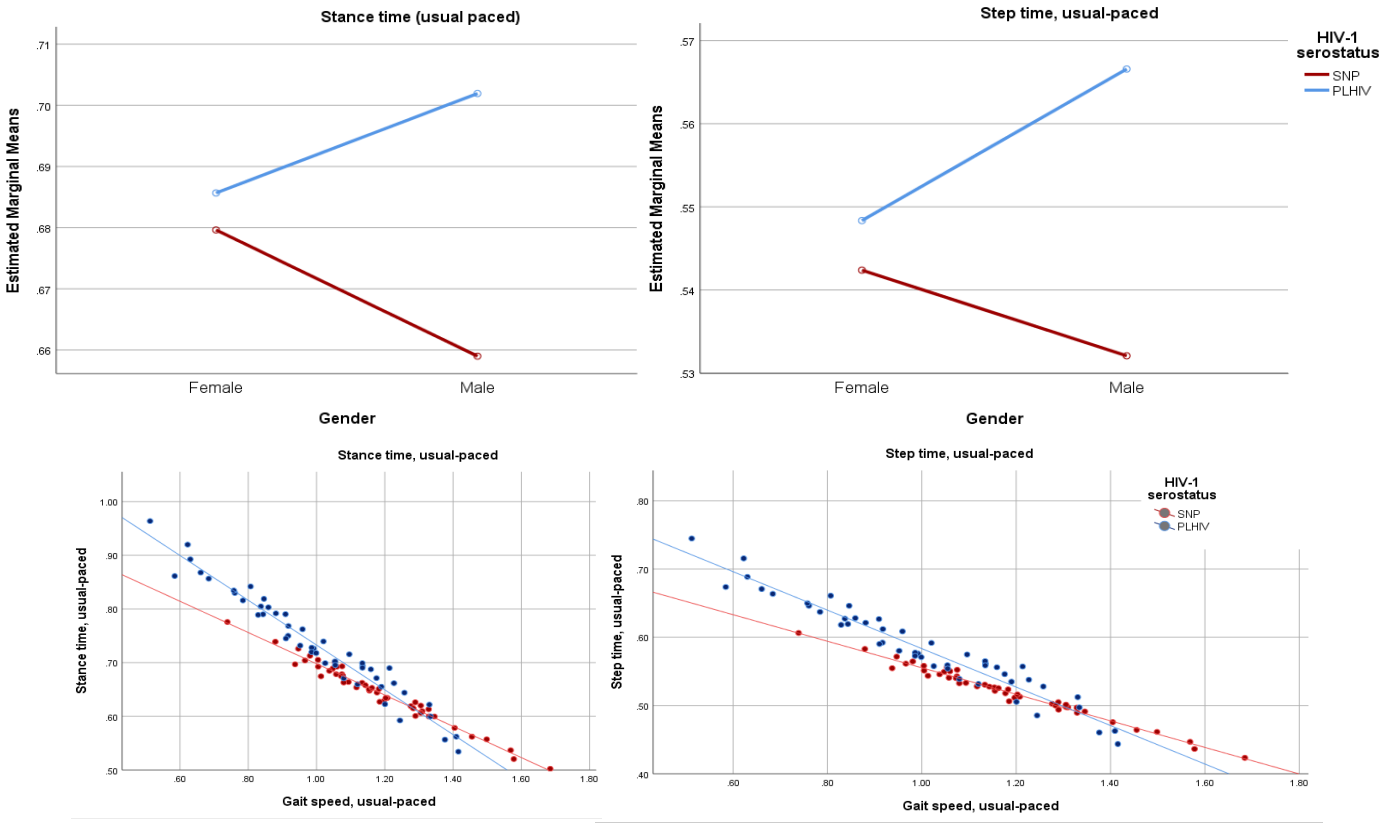

Figure 8.5. Interaction effects noted between HIV-serostatus and gender, and HIV-serostatus and gait speed for stance and step time during usual-paced gait. For both outcomes, the effects of HIV seem larger in men; in addition, the effects of HIV seem more apparent at slower gait speeds.

Table 8.11.Temporal, spatial, temporophasic and temporospatial parameters during usual-paced gait in PLHIV and SNP. Blue arrows indicate the directional trend of the difference in PLHIV relative to SNP.

Group	n	Unadjusted			Adjusted		
		Mean ± SD (95% CI)	Difference (95% CI)	p-value	Mean ± SE (95% CI)	Difference (95% CI)	p-value
Step length (cm)							
PLHIV	50	57.52 ± 7.66 (55.35; 59.70)	-3.65 ± 1.41 (-6.44; -0.90)	**0.011**↓	60.55 ± 0.56 (59.44; 61.65)	1.30 ± 0.85 (-0.38; 3.00)	0.127↑
SNP	48	61.17 ± 6.14 (59.38; 62.95)			59. 24 ± 0.61 (58.03; 60.45)		
Normalised step length‡							
PLHIV	50	0.73 ± 0.08 (0.71; 0.75)	-0.06 ± 0.02 (-0.09; -0.03)	**0.001**↓	0.76 ± 0.006 (0.75; 0.77)	0.01 ± 0.01 (-0.01; 0.03)	0.297↑
SNP	48	0.79 ± 0.08 (0.76; 0.81)			0.75 ± 0.007 (0.74; 0.76)		
Stride length (cm)							
PLHIV	50	113.21 ± 15.96 (108.67; 117.74)	-7.79 ± 2.86 (-13.47; -2.11)	**0.008**↓	119.36 ± 1.11 (117.15; 121.58)	2.41 ± 1.70 (-0.96; 5.77)	0.159↑
SNP	48	121.0 ± 12.03 (117.50; 124.49)			116.96 ± 1.22 (114.54; 119.38)		
Normalised stride length							
PLHIV	50	1.44 ± 0.18 (1.39; 1.49)	-0.12 ± 0.03 (-0.18; 0.05)	**<0.001**↓	1.50 ± 0.01 (1.48; 1.53)	0.03 ± 0.02 (-0.01; 0.07)	0.122↑
SNP	48	1.56 ± 0.15 (1.51; 1.60)			1.47 ± 0.02 (1.44; 1.50)		
Cadence (steps/min)							
PLHIV	50	104.48 ± 12.64 (100.89; 108.07)	-11.86 ± 2.31 (-16.44; 7.28)	**<0.001**↓	109.69 ± 0.85 (108.01; 111.37)	-2.06 ± 1.26 (-4.57; 0.45)	0.106↓

SNP	48	116.34 ± 9.99 (113.44; 119.24)			111.75 ± 0.86 (110.04; 113.46)		
Normalised cadence							
PLHIV	50	29.61 ± 3.74 (28.55; 30.68)	-3.15 ± 0.68 (-4.51; 1.80)	**<0.001**↓	31.05 ± 0.24 (30.57; 31.52)	-0.51 ± 0.36 (-1.21; 0.20)	0.155↓
SNP	48	32.77 ± 2.98 (31.91; 33.63)			31.55 ± 0.24 (31.07; 32.03)		
Stance time (sec)							
PLHIV	50	0.73 ± 0.10 (0.71; 0.76)	0.09 ± 0.02 (0.05; 0.12)	**<0.001**↑	0.69 ± 0.01 (0.68; 0.71)	0.02 ± 0.01 (0.001; 0.03)	**0.038**↑
SNP	48	0.65 ± 0.06 (0.63; 0.67)			0.67 ± 0.01 (0.66; 0.68)		
Step time (sec)							
PLHIV	50	0.59 ± 0.07 (0.56; 0.61)	0.06 ± 0.01 (0.04; 0.09)	**<0.001**↑	0.55 ± 0.004 (0.55; 0.56)	0.02 ± 0.01 (0.002; 0.03)	**0.023**↑
SNP	48	0.52 ± 0.04 (0.51; 0.53)			0.54 ± 0.01 (0.53; 0.55)		
Single support time (sec)							
PLHIV	50	0.44 ± 0.05 (0.42; 0.45)	0.04 ± 0.01 (0.03; 0.06)	**<0.001**↑	0.42 ± 0.004 (0.41; 0.43)	0.01 ± 0.01 (-0.001; 0.03)	0.077↑
SNP	48	0.39 ± 0.03 (0.38; 0.40)			0.41 ± 0.01 (0.40; 0.42)		
Double support time (sec)							
PLHIV	50	0.29 (0.09) (0.25; 0.34)#	0.05 ± 0.01 (0.02; 0.07)	**<0.001**↑	0.28 ± 0.01 (0.27; 0.29)	0.003 ± 0.01 (-0.01; 0.02)	0.667↑
SNP	48	0.24 (0.06) (0.22; 0.27)#			0.27 ± 0.01 (0.26; 0.28)		

Stance time (%GC)							
PLHIV	50	62.64 (2.36) (61.50; 63.86)[#]	0.65 ± 0.34 (-0.03; 1.33)	**0.031**↑	62.21 ± 0.21 (61.79; 62.62)	-0.11 ± 0.32 (-0.74; 0.53)	0.733↓=
SNP	48	61.67 (2.39) (60.82; 63.20)			62.32 ± 0.23 (61.86; 62.77)		
Single support time (%GC)							
PLHIV	50	37.37 ± 1.72 (36.88; 37.85)	-0.55 ± 0.38 (-1.31; 0.21)	0.153↓	37.87 ± 0.24 (37.39; 38.35)	0.22 ± 0.37 (-0.52; 0.95)	0.562↑
SNP	48	37.92 ± 2.04 (37.32; 38.51)			37.66 ± 0.27 (37.13; 38.19)		
Double support time (%GC)							
PLHIV	50	25.26 (3.76) (23.24; 27.00)[#]	1.20 ± 0.69 (-0.18; 2.58)	**0.042**↑	24.33 ± 0.43 (23.49; 25.18)	0.32 ± 0.72 (-1.11; 1.76)	0.655↓
SNP	48	23.48 (4.72) (21.80; 26.53)[#]			24.66 ± 0.47 (23.73; 25.59)		
Gait speed (m/s)[†]							
PLHIV	50	0.99 ± 0.22 (0.93; 1.06)	-0.18 ± 0.04 (-0.30; -0.10)	**<0.001**↓	1.01 ± 0.03 (0.95; 1.07	-0.17 ± 0.04 (-0.26; -0.08)	**<0.001**↓
SNP	48	1.18 ± 0.19 (1.12; 1.23)			1.18 ± 0.03 (1.12; 1.24)		
Normalised gait speed[†]							
PLHIV	50	0.36 ± 0.08 (0.33; 0.38)	-0.07 ± 0.01 (-0.10; -0.04)	**<0.001**↓	0.36 ± 0.01 (0.34; 0.38)	-0.06 ± 0.02 (-0.09; -0.03)	**0.001**↓
SNP	48	0.43 ± 0.07 (0.41; 0.45)			0.42 ± 0.01 (0.40; 0.45)		

Abbreviations: CI = confidence interval; n = number of participants; PLHIV = people living with HIV-1 infection; SD = standard deviation; SE = standard error; sec = seconds; SNP = HIV-seronegative participants.

Covariables in the adjusted model were gender, age and leg-length normalised gait speed.

[#]*presented as median (IQR) (Q1 – Q3); p-value obtained via Mann-Whitney U test.*

[‡]*Since normalised step and stride length were already scaled to leg length, the models for these outcomes included unadjusted gait speed as covariable.*

[†]*Gait speed and normalised gait speed were only adjusted for gender and age.*

8.5.1.2. Fast-paced gait

Unadjusted comparisons showed that differences in unadjusted gait speed were no longer significant in fast-paced gait ($p = 0.050$), although normalised gait speed remained significantly slower in PLHIV ($p = 0.032$). Spatial parameters and temporophasic parameters no longer differed significantly between PLHIV and SNP, but temporal and temporospatial parameters including cadence, normalised cadence (both decreased in PLHIV), stance time, step time, single support time and double support time in seconds (all increased in PLHIV) differed significantly between PLHIV and SNP ($p < 0.05$).

Adjusted analysis rendered all TSP differences non-significant between groups, except for step time, which was increased in PLHIV relative to SNP Full results are presented in Table 8.12.

Table 8.12. Temporal, spatial, temporophasic and temporospatial parameters during fast-paced gait in PLHIV and SNP. Blue arrows indicate the directional trend of the difference in PLHIV relative to SNP.

Group	n	Unadjusted			Adjusted		
		Mean ± SD (95% CI)	Difference (95% CI)	*p*-value	Mean ± SE (95% CI)	Difference (95% CI)	*p*-value
Step length (cm)							
PLHIV	45	69.36 ± 10.08 (66.33; 72.39)	-1.62 ± 1.78 (-5.15; 1.91)	0.365↓	71.42 ± 0.62 (70.19; 72.64)	1.10 ± 0.88 (-0.65; 2.85)	0.216↑
SNP	45	70.98 ± 6.37 (69.06; 72.89)			70.32 ± 0.65 (69.02; 71.62)		
Normalised step length‡							
PLHIV	45	0.88 ± 0.10 (0.85; 0.91)	-0.03 ± 0.02 (-0.07; 0.01)	0.172↓	0.90 ± 0.01 (0.88; 0.92)	0.01 ± 0.01 (-0.02; 0.03)	0.583↑
SNP	45	0.91 ± 0.08 (0.89; 0.94)			0.89 ± 0.01 (0.87; 0.91)		
Stride length (cm)							
PLHIV	45	137.18 ± 20.73 (130.95; 143.40)	-3.24 ± 3.60 (-10.39; 3.91)	0.370↓	141.37 ± 1.27 (138.85; 143.89)	2.08 ± 1.81 (-1.52; 5.69)	0.253↑
SNP	45	140.42 ± 12.37 (136.70; 144.13)			139.29 ± 1.34 (136.62; 142.0)		
Normalised stride length							
PLHIV	45	1.75 ± 0.21 (1.68; 1.81)	-0.06 ± 0.04 (-0.13; 0.02)	0.169↓	1.78 ± 0.02 (1.75; 1.81)	0.01 ± 0.02 (0.04; 0.06)	0.611↑
SNP	45	1.80 ± 0.16 (1.75; 1.85)			1.77 ± 0.02 (1.73; 1.80)		

Cadence (steps/min)							
PLHIV	45	132.24 ± 14.57 (127.86; 136.61)	-8.47 ± 2.82 (-14.07; -2.86)	**0.004**↓	134.43 ± 1.08 (132.282; 136.58)	-2.73 ± 1.54 (-5.80; 0.34)	0.080↓
SNP	45	140.70 ± 12.08 (137.07; 144.33)			137.16 ± 1.14 (134.90; 139.43)		
Normalised cadence							
PLHIV	45	37.39 ± 4.42 (36.06; 38.71)	-2.27 ± 0.82 (-3.89; 0.64)	**0.007**↓	38.07 ± 0.30 (37.48; 38.66)	-0.76 ±0.43 (-1.60; 0.09)	0.067↓
SNP	45	39.65 ± 3.23 (38.68; 40.62)			38.82 ± 0.32 (38.20; 39.45)		
Stance time (sec)							
PLHIV	45	0.55 ± 0.08 (0.53; 0.58)	0.04 ± 0.01 (0.01; 0.07)	**0.004**↑	0.54 ± 0.01 (0.53; 0.55)	0.01 ± 0.01 (-0.001; 0.03)	0.076↑
SNP	45	0.51 ± 0.05 (0.50; 0.53)			0.53 ± 0.01 (0.52; 0.54)		
Step time (sec)							
PLHIV	45	0.46 ± 0.05 (0.45; 0.48)	0.03 ± 0.01 (0.01; 0.05)	**0.002**↑	0.46 ± 0.004 (0.45; 0.46)	0.01 ± 0.01 (0.001; 0.02)	**0.039**↑
SNP	45	0.43 ± 0.04 (0.42; 0.44)			0.44 ± 0.004 (0.43; 0.45)		
Single support time (sec)							
PLHIV	45	0.37 ± 0.03 (0.36; 0.38)	0.02 ± 0.01 (0.006; 0.03)	**0.003**↑	0.37 ± 0.003 (0.36; 0.37)	0.01 ± 0.01 (0.00; 0.02)	0.065↑
SNP	45	0.34 ± 0.02 (0.34; 0.36)			0.36 ± 0.004 (0.35; 0.36)		
Double support time (sec)							
PLHIV	45	0.19 ± 0.05 (0.17; 0.20)	0.02 ± 0.01 (0.003; 0.04)	**0.026**↑	0.18 ± 0.004 (0.17; 0.19)	0.01 ± 0.01 (-0.01; 0.02)	0.413↑

SNP	45	0.16 ± 0.04 (0.15; 0.18)			0.17 ± 0.004 (0.17; 0.18)		
Stance time (%GC)							
PLHIV	45	60.03 ± 1.99 (59.43; 60.63)	0.58 ± 0.40 (-0.21; 1.37)	0.147↑	59.65 ± 0.18 (59.30;60.00)	-0.05 ± 0.25 (-0.56; 0.45)	0.834↓
SNP	45	59.45 ± 1.76 (58.92; 59.98)			59.70 ± 0.19 (59.33;60.10)		
Single support time (%GC)							
PLHIV	45	40.04 ± 2.08 (39.41;40.66)	-0.59 ± 0.42 (-1.44; 0.25)	0.166↓	40.37 ± 0.22 (39.94;40.80)	0.05 ± 0.31 (-0.58; 0.67)	0.885↑
SNP	45	40.63 ± 1.95 (40.05;41.22)			40.33 ± 0.23 (39.87;40.79)		
Double support time (%GC)							
PLHIV	45	20.00 ± 4.00 (18.79;21.20)	-1.17 ± 0.80 (-2.75; 0.41)	0.144↑	19.28 ± 0.37 (18.55;20.01)	-0.10 ± 0.52 (-1.14; 0.94)	0.852↓
SNP	45	18.82 ± 3.53 (17.76;19.88)			19.38 ± 0.39 (18.60;20.15)		
Gait speed (m/s)†							
PLHIV	45	1.52 ± 0.35 (1.42;1.63)	-0.12 ± 0.06 (-0.24; 0.00)	0.050↓	1.55 ± 0.04 (1.47; 1.64)	-0.10 ± 0.06 (-0.22; 0.03)	0.120↓
SNP	45	1.64 ± 0.22 (1.58; 1.71)			1.65 ± 0.05 (1.56; 1.74)		
Normalised gait speed†							
PLHIV	45	0.55 ± 0.12 (0.51; 0.58)	-0.05 ± 0.02 (-0.09; - 0.004)	**0.032**↓	0.56 ± 0.02 (0.53; 0.59)	-0.04 ± 0.02 (-0.08; 0.01)	0.099↓
SNP	45	0.59 ± 0.08 (0.57; 0.62)			0.59 ± 0.02 (0.56; 0.63)		

Abbreviations: CI = confidence interval; n = number of participants; PLHIV = people living with HIV-1 infection; SD = standard deviation; SE = standard error; sec = seconds; SNP = HIV-seronegative participants.
Covariables in the adjusted model were gender, age and leg-length normalised gait speed.
‡Since normalised step and stride length were already scaled to leg length, the models for these outcomes included unadjusted gait speed as covariable.
†Gait speed and normalised gait speed were only adjusted for gender and age.

8.5.1.3. Dual task gait

Table 8.13 presents results for TSPs measured under dual task conditions. As expected, gait speed was slower in both groups compared to usual-paced gait. Unadjusted comparisons demonstrated a similar pattern in TSP differences as described for usual-paced gait, namely significantly reduced gait speed in PLHIV relative to SNP, with decreased spatial parameters and cadence in PLHIV, and generally increased temporal and temporophasic parameters. Whereas single support time as a percentage of the gait cycle was the only non-significant between-group difference for usual-paced gait, dual task conditions led to stance time as a percentage of the gait cycle being the only non-significant difference. Adjusted analysis rendered all TSP differences non-significant, except for gait speed, normalised gait speed and stride length - which were increased in PLHIV along with a significantly increased step time (p-value for analysis with robust HC3 SE = 0.022). A significant interaction was noted for HIV-serostatus and gait speed (F = 22.10, $p < 0.001$) on step time, as illustrated in Figure 8.6.

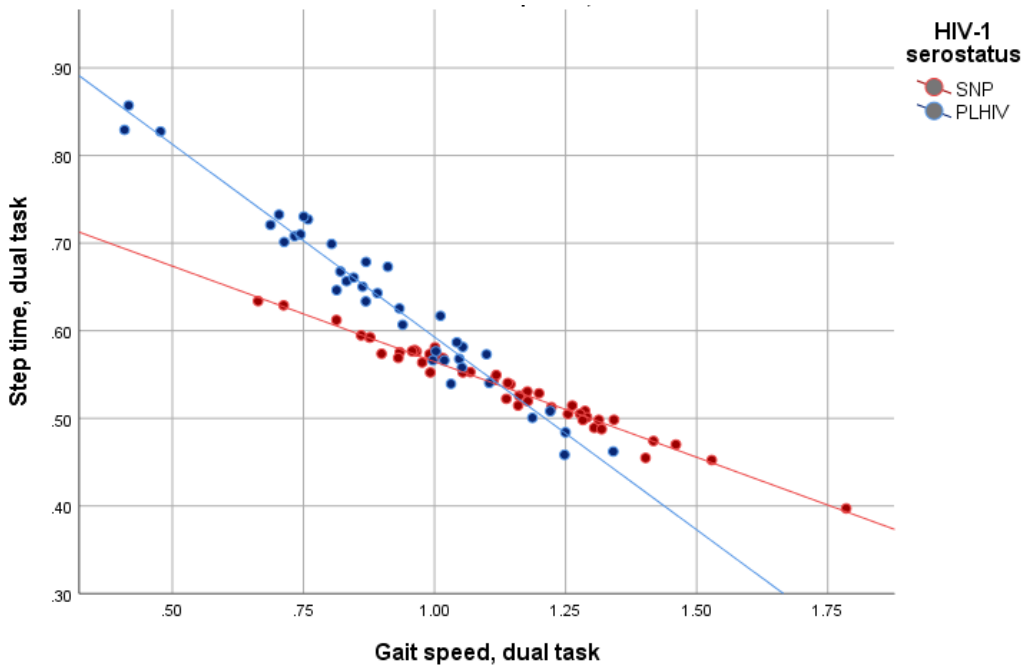

Figure 8.6. Grouped scatter plot demonstrating the interaction effect between HIV-serostatus and gait speed on step time during dual task conditions, showing that the detrimental effect of HIV-serostatus is particularly apparent at slow speeds.

Table 8.13. Temporal, spatial, temporophasic and temporospatial parameters during dual task gait in PLHIV and SNP. Blue arrows indicate the directional trend of the difference in PLHIV relative to SNP.

Group	n	Unadjusted			Adjusted		
		Mean ± SD (95% CI)	Difference (95% CI)	*p*-value	Mean ± SE (95% CI)	Difference (95% CI)	*p*-value
Step length (cm)							
PLHIV	39	56.03 ± 7.46 (53.61; 58.45)	-4.19 ± 1.56 (-7.30; 1.08)	**0.009**↓	59.81 ± 0.74 (58.34; 61.28)	2.00 ± 1.05 (-0.10; 4.10)	0.061↑
SNP	47	60.22 ± 7.00 (58.16;62.27)			57.81 ± 0.72 (56.38; 59.23)		
Normalised step length‡							
PLHIV	39	0.72 ± 0.09 (0.69; 0.75)	-0.06 ± 0.02 (-0.10; -0.02)	**0.003**↓	0.76 ± 0.01 (0.74; 0.78)	0.02 ± 0.01 (-0.01; 0.05)	0.122↑
SNP	47	0.78 ± 0.09 (0.75; 0.80)			0.74 ± 0.010 (0.72; 0.76)		
Stride length (cm)							
PLHIV	39	109.96 ± 15.99 (104.78; 115.14)	-8.45 ± 3.24 (-14.89; -2.00)	**0.011**↓	117.99 ± 1.50 (115.00; 120.97)	4.50 ± 2.14 (0.25; 8.76)	**0.038**↑
SNP	47	118.41 ± 14.06 (114.28; 122.54)			113.48 ± 1.46 (110.59; 116.38)		
Normalised stride length							
PLHIV	39	1.41 ± 0.19 (1.35; 1.47)	-0.12 ± 0.04 (-0.20; 0.04)	**0.005**↓	1.50 ± 0.02 (1.46; 1.54)	0.05 ± 0.03 (-0.01; 0.10)	0.088↑
SNP	47	1.53 ± 0.19 (1.47; 1.58)			1.45 ± 0.02 (1.41; 1.49)		

Cadence (steps/min)							
PLHIV	39	97.37 ± 15.43 (92.37; 102.37)	-16.07 ± 2.96 (-21.95; -10.19)	**<0.001**↓	106.11 ± 1.32 (103.48; 108.74)	-3.76 ± 1.90 (-7.56; 0.04)	0.052↓
SNP	47	113.44 ± 11.99 (109.92; 116.96)			109.87 ± 1.38 (107.13; 112.62)		
Normalised cadence							
PLHIV	39	27.52 ± 4.60 (26.02; 29.01)	-4.38 ± 0.86 (-6.09; -2.67)	**<0.001**↓	30.18 ± 0.40 (29.39; 30.97)	-1.06 ± 0.58 (-2.20 ±0.09)	0.071↓
SNP	47	31.90 ± 3.34 (30.92; 32.88)			31.24 ± 0.42 (30.41; 32.06)		
Stance time (sec)							
PLHIV	39	0.80 ± 0.15 (0.76; 0.85)	0.14 ± 0.02 (0.09; 0.19)	**<0.001**↑	0.72 ± 0.01 (0.70; 0.74)	0.02 ± 0.01 (0.00; 05)	0.100↑
SNP	47	0.67 ± 0.08 (0.64; 0.69)			0.70 ± 0.01 (0.68; 0.72)		
Step time (sec)							
PLHIV	39	0.61 (0.16) (0.54; 0.70)	0.10 ± 0.02 (0.06; 0.14)	**<0.001**↑	0.57 ± 0.01 (0.56; 0.59)	-0.19 ± 0.08$ (-0.35; -0.33)	**0.022$**↑
SNP	47	0.54 (0.08) (0.50; 0.58)			0.56 ± 0.01 (0.54; 0.57)		
Single support time (sec)							
PLHIV	39	0.45 (0.09) (0.42; 0.51)	0.06 ± 0.01 (0.04; 0.09)	**<0.001**↑	0.44 ± 0.01 (0.43; 0.46)	0.02 ± 0.01 (0.00; 0.04)	0.098↑

SNP	47	0.41 (0.04) (0.38; 0.43)			0.43 ± 0.01 (0.41; 0.44)		
Double support time (sec)							
PLHIV	39	0.33 ± 0.08 (0.31; 0.36)	0.07 ± 0.01 (0.04; 0.10)	**<0.001**↑	0.29 ± 0.01 (0.27; 0.30)	0.01 ± 0.01 (0.01; 0.03)	0.371↑
SNP	47	0.26 ± 0.06 (0.25; 0.28)			0.28 ± 0.01 (0.27; 0.29)		
Stance time (%GC)							
PLHIV	39	62.95 ± 1.81 (62.37;63.54)	0.66 ± 0.41 (0.15; 1.46)	0.108↑	62.27 ± 0.29 (61.71;62.84)	-0.30 ±0.41 (-1.11; 0.51)	0.467↓
SNP	47	62.29 ± 1.92 (61.73;62.86)			62.57 ± 0.28 (62.02;63.12)		
Single support time (%GC)							
PLHIV	39	37.02 ± 1.72 (36.46;37.58)	-0.99 ± 0.39 (-1.78; -0.20)	**0.014**↓	37.60 ± 0.27 (37.06;38.14)	-0.05 ± 0.39 (0.82; 0.73)	0.904↓
SNP	47	38.00 ± 1.90 (37.45;38.56)			37.65 ± 0.26 (37.12;38.17)		
Double support time (%GC)							
PLHIV	39	25.93 ± 3.21 (24.89;26.97)	1.64 ± 0.75 (0.14; 3.14)	**0.032**↑	24.67 ± 0.52 (23.63;25.71)	-0.25 ± 0.74 (-1.73; 1.23)	0.738↓
SNP	47	24.29 ± 3.69 (23.21;25.37)			24.92 ± 0.51 (23.91;25.93)		
Gait speed (m/s)†							
PLHIV	39	0.90 ± 0.22 (0.83; 0.97)	-0.23 ± 0.05 (-0.32; -0.13)	**<0.001**↓	0.92 ± 0.04 (0.84 ±0.99)	-0.19 ± 0.05 (0.29; -0.09)	**<0.001**↓
SNP	47	1.13 ± 0.22 (1.06; 1.19)			1.11 ± 0.04 (1.03; 1.18)		

Normalised gait speed†							
PLHIV	39	0.32 ± 0.08 (0.30; 0.35)	-0.08 ± 0.02 (-0.12; -0.05)	**<0.001↓**	0.33 ± 0.01 (0.30; 0.36)	-0.07 ± 0.02 (-0.11; -0.03)	**<0.001↓**
SNP	47	0.41 ± 0.08 (0.39; 0.43)			0.40 ± 0.01 (0.37; 0.43)		

Abbreviations: CI = confidence interval; n = number of participants; PLHIV = people living with HIV-1 infection; SD = standard deviation; SE = standard error; sec = seconds; SNP = HIV-seronegative participants.
Covariables in the adjusted model were gender, age and leg-length normalised gait speed.
‡Since normalised step and stride length were already scaled to leg length, the models for these outcomes included unadjusted gait speed as covariable.
†Gait speed and normalised gait speed were only adjusted for gender and age.
$Estimated parameters with robust HC3 SEs due to a significant Levene's test (p = 0.020).

8.5.2. The enhanced Gait Variability Index (EGVI)

EGVI scores were calculated in 42 PLHIV and 37 SNP for the usual-paced condition, and in 40 PLHIV and 33 SNP for the dual task condition. EGVI calculation requires a minimum of five absolute differences (at least 13 consecutive steps per trial),[372,375] which necessitated the exclusion of some participant datasets. This was mainly the consequence of the myoMOTION system failing to detect consecutive gait events under very slow gait speeds. The EGVI was not calculated for fast-paced gait, due to problems with many participants not having enough valid *consecutive* strides per limb within a trial (e.g. many cycles demonstrated flight times, i.e. no period of double support). Calculating the EGVI for this condition would thus not have yielded a valid outcome in terms of gait variability for comparison.

When calculated under usual-paced conditions, mean ± SD EGVI scores in PLHIV (94.21 ± 9.55) were significantly lower (mean difference of -5.91 ± 1.94, 95% CI = -9.77 to -2.03, p = 0.003) compared to EGVI scores in SNP (which constituted the norm, i.e. 100.11 ± 7.73); indicating lower variability in PLHIV relative to what may be considered the norm in the sample.

When calculated under dual task conditions for both groups (retaining the same norm values as for the usual-paced condition), both groups demonstrated lower EGVI scores (less variability than what is considered the norm), with significantly lower scores (mean difference = -7.96 ± 2.29, 95% CI = -12.52 to -3.39, p = 0.001) for PLHIV (mean EGVI score = 89.67 ± 8.79) relative to SNP (mean EGVI score = 97.63 ± 10.46).

Usual-pace and dual task EGVI mean scores remained significantly lower in PLHIV after adjusting for age and gender (adjusted mean difference = -4.89 ± 2.39, p = 0.045, 95% CI = -9.66; -0.12 for usual pace and -8.86 ± 2.82, p = 0.003, 95% CI = -14.493; -3.234 for dual task).

8.5.3. Kinematic angles

8.5.3.1. Usual-paced gait

Unadjusted comparisons of joint/segment angles showed no significant differences between PLHIV and SNP for the pelvis, except for a significantly decreased range of pelvic obliquity in PLHIV. At the hip, PLHIV demonstrated significantly reduced flexion range during the gait cycle, peak flexion during swing, abduction range during midstance and adduction range during loading response.

At the knee, PLHIV also demonstrated smaller angles relative to SNP, with significantly decreased knee flexion range during the gait cycle and from stance to swing, as well as reduced peak knee flexion during swing.

The ankle joint demonstrated the largest between-group difference, namely 4.1°, this was the amount by which ankle plantarflexion during push-off was decreased in PLHIV relative to SNP. Other significant differences (decreased angles in PLHIV) included ankle dorsiflexion range during swing, ankle plantarflexion angle at toe-off and peak angle plantarflexion angle during the gait cycle.

Adjusting for age, gender and normalised gait speed revealed non-significant differences for all angles, although directional trends mostly remained the same. Nine out of the total of 28 measured angles showed a directional change: pelvic rotation ROM during the gait cycle, pelvic rotation at initial contact, hip flexion ROM during the gait cycle, hip flexion at initial contact, knee flexion ROM from stance to swing, knee flexion at initial contact, peak knee flexion during stance and during swing (all decreased in PLHIV relative to SNP prior to adjustment, and increased in PLHIV after adjustment), and peak hip flexion during swing (decreased in PLHIV relative to SNP prior to adjustment, and similar in both groups after adjustment). The largest difference between PLHIV and SNP was again observed for ankle plantarflexion ROM during push-off, which remained decreased in PLHIV, but not significantly so (mean difference = -2°, $p < 0.081$. Table 8.14 shows the full results for unadjusted and adjusted comparisons under usual-paced gait conditions.

Table 8.14. Kinematic lower limb angles and ROM during usual-paced gait in PLHIV and SNP. Blue arrows indicate the directional trend of the difference in PLHIV relative to SNP.

Group	n	Unadjusted			Adjusted		
		Mean ± SD (95% CI)	Difference (95% CI)	*p*-value	Mean ± SE (95% CI)	Difference (95% CI)	*p*-value
Pelvis tilt ROM during GC (°)							
PLHIV	50	4.3 (3.2)[#] (3.4; 6.5)	-0.7 (-0.1; 1.5)	0.084↓	5.3 ± 0.4 (4.5; 6.0)	-0.3 ± 0.5 (-1.4; 0.7)	0.544↓
SNP	48	5.2 (3.9)[#] (3.9; 7.8)			5.6 ± 0.4 (4.8; 6.4)		
Peak pelvis anterior tilt during GC (°)							
PLHIV	50	0.7 (5.1)[#] (-2.1; 3.0)	-0.8 (-0.6; 2.4)	0.286↓	0.2 ± 0.6 (-0.9; 1.3)	-0.2 ± 0.9 (-2.0; 1.7)	0.858↓
)SNP	48	1.4 (4.3)[#] (-0.3; 4.0)			0.4 ± 0.7 (-1.0; 1.7)		
Pelvis obliquity ROM during GC (°)							
PLHIV	50	10.1 ± 2.5 (9.4; 10.8)	-1.7 ± 0.6 (-2.8; 0.6)	**0.002**↓	10.4 ± 0.4 (9.6; 11.2)	-0.8 ± 0.6 (-1.9; 0.3)	0.151↓
SNP	48	11.9 ± 3.0 (11.0; 12.7)			11.2 ± 0.4 (10.4; 12.1)		
Pelvis rotation ROM during GC (°)							
PLHIV	50	13.2 ± 3.5 (12.2; 14.2)	-0.9 ± 0.8 (-2.5; 0.7)	0.271↓	13.6 ± 0.6 (12.5; 14.7)	0.5 ± 0.9 (-1.2; 2.3)	0.566↑
SNP	48	14.1 ± 4.4 (12.8; 15.3)			13.1 ± 0.7 (11.8; 14.4)		
Pelvis rotation angle at initial contact (°)							
PLHIV	50	4.2 (4.0)[#] (2.7; 6.7)	-0.1 (-1.2; 1.1)	0.921↓	4.6 ± 0.4 (3.8; 5.5)	0.2 ± 0.7 (-1.2; 1.5)	0.815↑

SNP	48	4.9 (3.6) [#] (2.6; 6.2)			4.5 ± 0.5 (3.5; 5.5)		
Hip flexion ROM during GC (°)							
PLHIV	50	38.8 ± 4.0 (37.6; 39.9)	-2.3 ± 0.8 (-4.0; 0.7)	**0.006**↓	40.0 ± 0.5 (39.1; 40.9)	0.9 ± 0.7 (0.6; 2.3)	0.236↑
SNP	48	41.1 ± 4.1 (39.9; 42.3)			39.1 ± 0.5 (38.0; 40.2)		
Hip flexion ROM during loading response (°)							
PLHIV	50	7.7 ± 2.4 (7.0; 8.4)	0.3 ± 0.5 (-0.7; 1.3)	0.529↑	7.3 ± 0.4 (6.6; 8.0)	0.2 ± 0.6 (-0.9; 1.4)	0.706↑
SNP	48	7.4 ± 2.7 (6.6; 8.1)			7.1 ± 0.4 (6.2; 8.0)		
Hip flexion ROM pre-swing to initial swing (°)							
PLHIV	50	8.0 ± 2.3 (7.4; 8.7)	0.4 ± 0.5 (-0.6; 1.4)	0.401↑	7.8 ± 0.4 (7.1; 8.5)	0.2 ± 0.6 (-1.0; 1.4)	0.765↑
SNP	48	7.6 ± 2.5 (6.9; 8.4)			7.6 ± 0.4 (6.8; 8.5)		
Hip flexion angle at initial contact (°)							
PLHIV	50	24.1 ± 5.3 (22.5; 25.6)	-2.0 ± 1.1 (-4.2; 0.2)	0.075↓	24.2 ± 0.7 (22.8; 25.5)	0.6 ± 1.0 (-1.5; 2.7)	0.561↑
SNP	48	26.1 ± 5.6 (24.4; 27.7)			23.6 ± 0.8 (22.1; 25.1)		
Peak hip flexion during swing (°)							
PLHIV	50	27.1 ± 5.1 (25.6; 28.5)	-2.7 ± 1.0 (-4.7; 0.7)	**0.009**↓	27.2 ± 0.6 (26.1; 28.4)	0.00	1.000=
SNP	48	29.8 ± 4.8 (28.4; 31.2)			27.2 ± 0.6 (26.0; 28.6)		

Peak hip extension during stance (°)							
PLHIV	50	11.5 ± 5.0 (10.0; 12.9)	0.3 ± 0.9 (-1.5; 2.1)	0.725↑	12.6 ± 0.5 (11.6; 13.7)	1.1 ± 0.9 (-0.6; 2.9)	0.201↑
SNP	48	11.1 ± 3.9 (10.0; 12.3)			11.5 ± 0.7 (10.2; 12.8)		
Hip abduction ROM during mid-stance (°)							
PLHIV	50	3.9 ± 1.6 (3.5; 4.4)	-1.2 ± 0.4 (-2.0; 0.4)	**0.002**↓	4.4 ± 0.2 (3.9; 4.9)	-0.2 ± 0.4 (-1.0; 0.6)	0.610↓
SNP	48	5.1 ± 2.1 (4.5; 5.8)			4.6 ± 0.3 (4.0; 5.1)		
Hip adduction ROM during loading response (°)							
PLHIV	50	6.2 ± 2.2 (5.6; 6.8)	-1.5 ± 0.5 (-2.5; 0.6)	**0.001**↓	6.4 0.3 (5.8; 7.0)	-0.5 ± 0.5 (-1.4; 0.4)	0.282↓
SNP	48	7.7 ± 2.4 (7.0; 8.4)			6.9 ± 0.3 (6.2; 7.5)		
Hip internal rotation ROM during GC (°)							
PLHIV	50	16.1 ± 4.0 (15.0; 17.3)	-1.0 ± 0.8 (-2.7; 0.6)	0.232↓	16.6 ± 0.6 (15.4; 17.8)	-0.7 ± 0.9 (-2.5; 1.2)	0.486↓
SNP	48	17.2 ± 4.3 (15.9; 18.4)			17.3 ± 0.7 (16.0; 18.6)		
Knee flexion ROM during GC (°)							
PLHIV	50	61.1(5.6) (57.7; 63.4)#	-2.6 (-4.3; 0.8)	**0.004**↓	61.4 ± 0.6 (60.1; 62.6)	-0.6 ± 0.9 (2.4; 1.2)	0.498↓
SNP	48	63.6 (5.8) (60.0; 65.8)#			62.0 ± 0.7 (60.6; 63.4)		
Knee flexion ROM during stance (°)							
PLHIV	50	10.1 ± 4.1 (8.9; 11.2)	-1.5 ± 0.8 (-3.1; 0.2)	0.078↓	11.1 ± 0.5 (10.0; 12.1)	-0.3 ± 0.8 (-2.0; 1.3)	0.689↓

SNP	48	11.5 ± 4.1 (10.4; 12.7)			11.4 ± 0.6 (10.2; 12.6)		
Knee flexion ROM from stance to swing (°)							
PLHIV	50	56.9 ± 4.9 (55.5; 58.3)	-2.5 ± 1.0 (-4.4; 0.6)	**0.012**↓	57.6 ± 0.6 (56.4; 58.8)	0.24 ± 0.9 (-1.6; 2.1)	0.801↑
SNP	48	59.4 ± 4.6 (58.1; 60.8)			57.4 ± 0.7 (56.0; 58.8)		
Knee extension ROM from mid-stance to terminal stance (°)							
PLHIV	50	8.9 ± 4.6 (7.6; 10.2)	-1.1 ± 1.0 (-3.1; 0.8)	0.250↓	10.0 ± 0.6 (8.7; 11.2)	0.9 ± 0.9 (-0.9; 2.7)	0.315↑
SNP	48	10.0 ± 5.1 (8.6; 11.5)			9.0 ± 0.7 (7.6; 10.4)		
Knee flexion at initial contact (°)							
PLHIV	50	4.8 ± 6.3 (3.0; 6.6)	-0.1 ± 1.1 (-2.3; 2.2)	0.961↓	5.1 ± 0.8 (3.5; 6.7)	1.5 ± 1.2 (-0.9; 4.0)	0.219↑
SNP	48	4.9 ± 4.6 (3.5; 6.2)			3.6 ± 0.9 (1.8; 5.3)		
Peak knee flexion during stance (°)							
PLHIV	50	43.1 ± 7.0 (41.2; 45.1)	-2.2 ± 1.2 (-4.6; 0.2)	0.069↓	43.6 ± 0.8 (42.0; 45.2)	0.2 ± 1.2 (-2.2; 2.7)	0.849↑
SNP	48	45.3 ± 4.7 (44.0; 46.7)			43.4 ± 0.9 (41.6; 45.2)		
Peak knee extension during stance (°)							
PLHIV	50	-3.4 ± 5.5 (-5.0; -1.9)	0.1 ± 0.9 (-1.7; 2.0)	0.899↑	-3.5 ± 0.7 (-4.9; -2.2)	-1.2 ± 1.0 (-3.2; 0.9)	0.250↑
SNP	48	-3.3 ± 3.4 (-4.3; -2.3)			-2.3 ± 0.7 (-3.8; -0.9)		

Peak knee flexion during swing (°)							
PLHIV	50	62.4 ± 7.2 (60.3; 64.4)	-3.1 ± 1.3 (-5.7; 0.5)	**0.018**↓	63.7 ± 0.8 (62.2; 65.3)	0.4 ± 1.2 (-1.9; 2.7)	0.713↑
SNP	48	65.5 ± 5.5 (64.0; 67.1)			63.3 ± 0.9 (61.5; 65.0)		
Ankle dorsiflexion ROM during stance (°)							
PLHIV	50	21.0 ± 3.2 (20.1; 22.0)	-0.3 ± 0.7 (-1.6; 1.0)	0.691↓	20.6 ± 0.5 (19.7; 21.5)	-0.9 ± 0.7 (-2.3; 0.5)	0.222↓
SNP	48	21.3 ± 3.3 (20.3; 22.3)			21.5 ± 0.5 (20.5; 22.5)		
Ankle dorsiflexion ROM during swing (°)							
PLHIV	50	16.9 ± 4.9 (15.5; 18.3)	-3.1 ± 1.0 (-5.1; 1.1)	**0.003**↓	18.0 ± 0.7 (16.5; 19.4)	-1.5 ± 1.1 (-3.7; 0.6)	0.159↓
SNP	48	20.0 ± 5.1 (18.6; 21.5)			19.5 ± 0.8 (17.9; 21.2)		
Ankle plantarflexion ROM, heel rise to toe-off (push off) (°)							
PLHIV	50	28.4 ± 5.2 (26.9; 29.9)	-4.1 ± 1.1 (-6.2; 2.0)	**0.001**↓	29.8 ± 0.7 (28.3; 31.2)	-2.0 ± 1.1 (-4.2; 0.2)	0.081↓
SNP	48	32.5 ± 5.4 (30.9; 34.0)			31.7 ± 0.8 (30.0; 33.4)		
Ankle dorsiflexion angle at initial contact (°)							
PLHIV	50	-8.6 (5.6) (-11.7; -6.1)#	0.8 (0.6; 2.2)	0.235↑	-8.7 ± 0.5 (-9.7; -7.8)	-0.1 ± 0.7 (-1.5; 1.2)	0.831↑
SNP	48	-8.2 (3.9) (-10.1; -6.2)#			-8.6 ± 0.5 (-9.6; -7.6)		
Ankle plantarflexion angle at toe-off (°)							
PLHIV	50	16.0 ± 6.0 (14.3; 17.7)	-3.0 ± 1.2 (-5.4; 0.7)	**0.012**↓	16.8 ± 0.8 (15.2; 18.5)	-0.9 ± 1.2 (-3.4; 1.6)	0.462↓
SNP	48	19.0 ± 5.6 (17.4; 20.7)			17.8 ± 0.9 (16.0; 19.6)		

Peak ankle plantarflexion during GC (°)

PLHIV	50	18.9 ± 5.6 (17.3; 20.5)	-3.1 ± 1.2 (-5.3; 0.8)	**0.010**↓	19.5 ± 0.8 (17.9; 21.1)	-1.5 ± 1.3 (-4.0; 1.0)	0.224↓
SNP	48	21.9 ± 5.8 (20.2; 23.6)			21.0 ± 0.9 (19.2; 22.8)		

Abbreviations: CI = confidence interval; GC = gait cycle; n = number of participants; PLHIV = people living with HIV-1 infection; ROM = range of motion; SD = standard deviation; SE = standard error; SNP = HIV-seronegative participants.
Covariables included gender (male/female), age (in years) and normalised gait speed.
#presented as median (IQR) (Q1; Q3).

8.5.3.2. Fast-paced gait

At fast-paced gait (Table 8.15) no differences were apparent at the pelvis between PLHIV and SNP, while PLHIV demonstrated significantly decreased hip flexion range during the swing phase. At the knee, PLHIV achieved a smaller peak knee flexion angle during stance (i.e. during loading response) as well as a decreased peak knee flexion angle during swing. The only significant difference evident at the ankle was decreased dorsiflexion range during swing. The largest differences occurred at the ankle (dorsiflexion during swing, mean difference = -3°) and knee (peak flexion during swing, mean difference -3°). Adjusted analyses rendered all differences between PLHIV and SNP non-significant; the largest differences occurring at the knee (peak flexion during stance, decreased in PLHIV, mean difference = -1.5°, p = 0.169) and pelvis (rotation range during the gait cycle, increased in PLHIV, mean difference = 1.6°, p =0.088).

Table 8.15. Kinematic lower limb angles and ROM during fast-paced gait in PLHIV and SNP. Blue arrows indicate the directional trend of the difference in PLHIV relative to SNP.

Group	n	Unadjusted			Adjusted		
		Mean ± SD (95% CI)	Difference (95% CI)	*p*-value	Mean ± SE (95% CI)	Difference (95% CI)	*p*-value
Pelvis tilt ROM during GC (°)							
PLHIV	45	6.2 (4.0)[#] (4.8; 8.8)	-0.3 (-0.7; 1.4)	0.506↓	7.2 ± 0.4 (6.4; 8.0)	0.3 ± 0.6 (-0.8; 1.5)	0.553↑
SNP	45	6.8 (3.7)[#] (5.2; 8.9)			6.8 ± 0.4 (6.0; 7.7)		
Peak pelvis anterior tilt during GC (°)							
PLHIV	45	1.8 ± 4.1 (0.7; 3.2)	-0.9 ± 0.9 (-2.7; 0.9)	0.343↓	1.8 ± 0.6 (0.6; 3.1)	0.0 ± 0.9 (-1.7; 1.8)	0.964=
SNP	45	2.8 ± 4.5 (1.5; 4.2)			1.8 ± 0.7 (0.5; 3.1)		
Pelvis obliquity ROM during GC (°)							
PLHIV	45	13.3 ± 3.4 (12.3; 14.3)	-0.8 ± 0.7 (-2.2; 0.6)	0.279↓	13.7 ± 0.5 (12.8; 14.6)	0.4 ± 0.6 (-0.9; 1.6)	0.584↑
SNP	45	14.1 ± 3.3 (13.1; 15.1)			13.3 ± 0.5 (12.4; 14.3)		
Pelvis rotation ROM during GC (°)							
PLHIV	45	16.3 (4.9)[#] (14.4; 19.2)	-0.4 (-2.4; 1.8)	0.678↓	17.04 ± 0.6 (15.8; 18.3)	1.6 ± 1.0 (-0.2; 3.4)	0.088↑
SNP	45	16.4 (7.8) (12.7; 20.4)			15.4 ± 0.7 (14.1; 16.8)		
Pelvis rotation angle at initial contact (°)							
PLHIV	45	5.5 (2.9)[#] (3.8; 6.7)	0.4 (-1.6; 0.7)	0.446↑	5.7 ± 0.6 (4.7; 6.7)	0.8 ± 0.8 (-0.7; 2.4)	0.289↑
SNP	45	5.3 (4.3)[#] (2.7; 7.0)			4.9 ± 0.6 (3.7; 6.0)		

Hip flexion ROM during GC (°)							
PLHIV	45	45.3 ± 4.9 (43.9; 46.8)	-1.2 ± 1.0 (-3.2; 0.7)	0.219↓	45.9 ± 0.5 (44.8; 46.9)	0.4 ± 0.7 (-1.1; 1.9)	0.585↑
SNP	45	46.6 ± 4.4 (45.2; 47.9)			45.5 ± 0.5 (44.4; 46.5)		
Hip flexion ROM during loading response (°)							
PLHIV	45	6.1 (3.2)# (4.6; 7.8)	0.68 (-0.3; 1.6)	0.179↑	5.7 ± 0.3 (5.1; 6.4)	0.4 ± 0.5 (-0.5; 1.4)	0.373↑
SNP	45	5.4 (3.2)# (3.7; 6.9)			5.3 ± 0.4 (4.6; 6.0)		
Hip flexion ROM pre-swing to initial swing (°)							
PLHIV	45	6.5 ± 2.5 (5.7; 7.2)	-0.2 ± 0.5 (-1.2; 0.8)	0.677↓	6.1 ± 0.3 (5.4; 6.8)	-0.4 ± 0.5 (-1.4; 0.6)	0.387↓
SNP	45	6.7 ± 2.3 (6.0; 7.4)			6.6 ± 0.4 (5.8; 7.3)		
Hip flexion angle at initial contact (°)							
PLHIV	45	28.6 ± 5.9 (26.9; 30.4)	-1.8 ± 1.2 (-4.2; 0.5)	0.123↓	28.6 ± 0.7 (27.2; 30.0)	0.1 ± 1.0 (-1.9; 2.1)	0.934=
SNP	45	30.5 ± 5.3 (28.9; 32.1)			28.5 ± 0.8 (27.0; 30.0)		
Peak hip flexion during swing (°)							
PLHIV	45	31.0 ± 5.6 (29.3; 32.7)	-2.7 ± 1.2 (-5.1; 0.3)	**0.028**↓	30.8 ± 0.7 (29.5; 32.1)	-0.4 ± 0.9 (-2.3; 1.5)	0.650↓
SNP	45	33.7 ± 5.7 (32.0; 35.4)			31.2 ± 0.7 (29.8; 32.6)		
Peak hip extension during stance (°)							
PLHIV	45	13.5 (8.9)# (10.0; 18.9)	1.3 (-0.8; 3.4)	0.228↑	14.6 ± 0.9 (12.8; 16.4)	1.1 ± 1.2 (-1.4; 3.6)	0.431↑
SNP	45	11.9 (5.6)# (9.6; 15.2)			13.5 ± 0.9 (11.8; 15.3)		

Hip abduction ROM during mid-stance (°)

PLHIV	45	6.8 ± 2.3 (6.1; 7.5)	-0.9 ± 0.5 (-1.9; 0.2)	0.096↓	7.1 ± 0.3 (6.4; 7.8)	-0.2 ± 0.5 (-1.1; 0.8)	0.733↓
SNP	45	7.7 ± 2.7 (6.9; 8.5)			7.3 ± 0.4 (6.6; 8.0)		

Hip adduction ROM during loading response (°)

PLHIV	45	6.7 ± 2.2 (6.0; 7.3)	-0.4 ± 0.5 (-1.3; 0.5)	0.352↓	6.6 ± 0.3 (6.0; 7.3)	-0.3 ± 0.5 (-1.2; 0.6)	0.533↓
SNP	45	7.1 ± 2.1 (6.5; 7.7)			6.9 ± 0.3 (6.2; 7.6)		

Hip internal rotation ROM during GC (°)

PLHIV	45	18.3 ± 3.9 (17.1; 19.5)	-0.1 ± 0.9 (-1.8; 1.6)	0.901=	18.5 ± 0.6 (17.3; 19.8)	0.1 ± 0.9 (-1.7; 1.9)	0.926=
SNP	45	18.4 ± 4.4 (17.1; 16.7)			18.5 ± 0.7 (17.1; 19.8)		

Knee flexion ROM during GC (°)

PLHIV	45	62.9 ± 4.5 (61.5; 64.2)	-1.3 ± 0.9 (-3.2; 0.6)	0.164↓	63.2 ± 0.6 (62.0; 64.3)	0.4 ± 0.8 (-1.3; 2.0)	0.655↑
SNP	45	64.2 ± 4.6 (62.8; 65.6)			62.8 ± 0.6 (61.6; 64,0)		

Knee flexion ROM during stance (°)

PLHIV	45	13.1 ± 4.22 (11.8; 14.4)	-0.5 ± 0.8 (-2.1; 1.2)	0.590↓	13.9 ± 0.5 (12.8; 14.9)	-0.7 ± 0.8 (-2.3; 0.8)	0.334↓
SNP	45	13.6 ± 3.8 (12.4; 14.7)			14.6 ± 0.6 (13.5; 15.7)		

Knee flexion ROM from stance to swing (°)

PLHIV	45	61.3 ± 5.1 (59.7; 62.8)	-1.6 ± 1.1 (-3.8; 0.5)	0.135↓	61.5 ± 0.6 (60.3; 62.7)	0.4 ± 0.9 (-1.3; 2.2)	0.613↑
SNP	45	62.9 ± 5.1 (61.4; 64.5)			61.1 ± 0.6 (59.8; 62.4)		

Knee extension ROM from mid-stance to terminal stance (°)							
PLHIV	45	16.7 ± 5.8 (15.0; 18.4)	-0.6 ± 1.1 (-2.8; 1.7)	0.618↓	17.8 ± 0.7 (16.5; 19.1)	0.3 ± 0.9 (1.6; 2.2)	0.737↑
SNP	45	17.27 ± 4.9 (15.8; 18 .7)			17.5 ± 0.7 (16.1; 18.9)		
Knee flexion at initial contact (°)							
PLHIV	45	7.5 ± 6.8 (5.5; 9.5)	-1.5 ± 1.3 (-4.5; 1.0)	0.235↓	7.5 ± 0.9 (5.8; 9.2)	-0.1 ± 1.3 (-2.6; 2.4)	0.941↓
SNP	45	9.0 ± 5.0 (7.5; 10.5)			7.6 ± 09 (5.7; 9.4)		
Peak knee flexion during stance (°)							
PLHIV	45	41.9 ± 6.4 (40.0; 43.8)	-2.4 ± 1.2 (-4.8; 0.1)	**0.041**↓	41.3 ± 0.8 (39.8; 42.8)	-1.5 ± 1.1 (-3.7; 0.7)	0.169↓
SNP	45	44.3 ± 4.6 (42.9; 45.7)			42.8 ± 0.8 (41.2; 44.5)		
Peak knee extension during stance (°)							
PLHIV	45	-2.7 (7.0)# (-6.5; 0.5)	1.4 (-0.5; 3.3)	0.141↓	-2.9 ± 0.6 (-4.2; -1.7)	0.8 ± 0.9 (-0.9; 2.6)	0.357↓
SNP	45	-3.9 (3.7)# (-6.0; -2.2)			-3.8 ± 0.7 (-5.1; -2.5)		
Peak knee flexion during swing (°)							
PLHIV	45	65.1 ± 6.7 (63.1; 67.1)	-3.0 ± 1.3 (-5.5; 0.5)	**0.020**↓	65.2 ± 0.7 (63.7; 66.6)	-0.8 ± 1.0 (-2.9; 1.2)	0.426↓
SNP	45	68.1 ± 5.3 (66.5; 69.7)			66.0 ± 0.8 (64.5; 67.6)		
Ankle dorsiflexion ROM during stance (°)							
PLHIV	45	16.9 ± 3.6 (15.8; 18.0)	0.5 ± 0.8 (-1.0; 2.0)	0.533↑	16.6 ± 0.5 (15.6; 17.5)	-0.30 ± 0.7 (-1.7; 1.1)	0.664↓
SNP	45	16.4 ± 3.5 (15.3; 17.5)			16.9 ± 0.5 (15.8; 17.9)		

Ankle dorsiflexion ROM during swing (°)							
PLHIV	45	20.7 ± 6.3 (18.9; 22.6)	-3.0 ± 1.2 (-5.4; 0.5)	**0.019**↓	21.4 ± 0.8 (19.9; 23.0)	-1.4 ± 1.1 (-3.6; 0.9)	0.238↓
SNP	45	23.7 ± 5.5 (22.0; 25.3)			22.8 ± 0.9 (21.1; 24.5)		
Ankle plantarflexion ROM, heel rise to toe-off (push off) (°)							
PLHIV	45	29.3 ± 5.3 (27.7; 30.9)	-2.0 ± 1.1 (-4.2; 0.1)	0.063↓	29.7 ± 0.7 (28.2; 31.2)	-1.3 ± 1.1 (-3.5; 0.8)	0.219↓
SNP	45	31.3 ± 5.0 (29.8; 32.8)			31.1 ± 0.8 (29.5; 32.7)		
Ankle dorsiflexion angle at initial contact (°)							
PLHIV	45	-7.4 ± 3.3 (-8.4; -6.4)	-1.1 ± 0.7 (-2.4; 0.2)	0.103↑	-7.3 ± 0.5 (-8.3; -6.4)	-0.4 ± 0.7 (-1.7; 1.0)	0.569↑
SNP	45	-6.3 ± 3.0 (-7.2; -5.4)			-6.9 ± 0.5 (-7.9; -5.9)		
Ankle plantarflexion angle at toe-off (°)							
PLHIV	45	20.0 ± 6.7 (18.0; 22.0)	-1.5 ± 1.3 (-4.0; 1.1)	0.255↓	20.7 ± 0.9 (18.9; 22.5)	-0.2 ± 1.3 (-2.7; 2.3)	0.874↓
SNP	45	21.5 ± 5.5 (19.9; 23.2)			20.9 ± 1.0 (19.0; 22.8)		
Peak ankle plantarflexion during GC (°)							
PLHIV	45	22.0 ± 6.5 (20.0; 24.0)	-1.5 ± 1.3 (-4.0; 1.1)	0.251↓	22.6 ± 0.9 (20.8; 24.4)	-0.4 ± 1.3 (-3.0; 2.2)	0.748↓
SNP	45	23.5 ± 5.7 (21.7; 25.2)			23.1 ± 0.1 (21.1; 25.0)		

Abbreviations: CI = confidence interval; GC = gait cycle; n = number of participants; PLHIV = people living with HIV-1 infection; ROM = range of motion; SD = standard deviation; SE = standard error; SNP = HIV-seronegative participants.
Covariables included gender (male/female), age (in years) and normalised gait speed.
[#]presented as median (IQR) (Q1; Q3).

8.5.3.3. Dual task gait

Figure 8.7 illustrates the kinematic curves (unadjusted data) for PLHIV and SNP. Unadjusted comparisons of kinematic angles for dual task gait showed decreased pelvis obliquity and rotation ranges during the gait cycle. Hip adduction range during loading response was also significantly decreased in PLHIV. At the knee, flexion range during the gait cycle and from stance to swing was significantly lower in PLHIV relative to SNP. Peak knee flexion during stance and during swing was also decreased in PLHIV. Ankle dorsiflexion range during swing was significantly reduced in PLHIV, as was ankle plantarflexion during push-off, ankle plantarflexion angle at toe-off and peak ankle plantarflexion during the gait cycle. The largest differences were noted for peak knee flexion during swing (mean difference = -4.6°), knee flexion range from stance to swing (mean difference = 4.8°) and knee flexion range during the gait cycle (mean difference is -4.6°).

Adjusted analyses showed PLHIV to have significantly higher pelvis rotation angles at initial contact. At the hip, an increase in both hip flexion ROM over the gait cycle and flexion angle at initial contact was noted. Total knee flexion range during the gait cycle was decreased, but knee flexion at initial contact was increased while knee extension range from mid-stance to terminal stance was increased, and peak knee extension in stance was also increased in PLHIV. No significant differences were noted at the ankle after adjustments were made. The largest difference observed was knee flexion angle at initial contact (increased in PLHIV, mean difference = 3.7°). Figure 8.7 shows the unadjusted gait curves and Table 8.16 the full unadjusted and adjusted comparison results. A significant interaction was noted between HIV-serostatus and gait speed on knee flexion range during the gait cycle; this interaction is demonstrated in Figure 8.8.

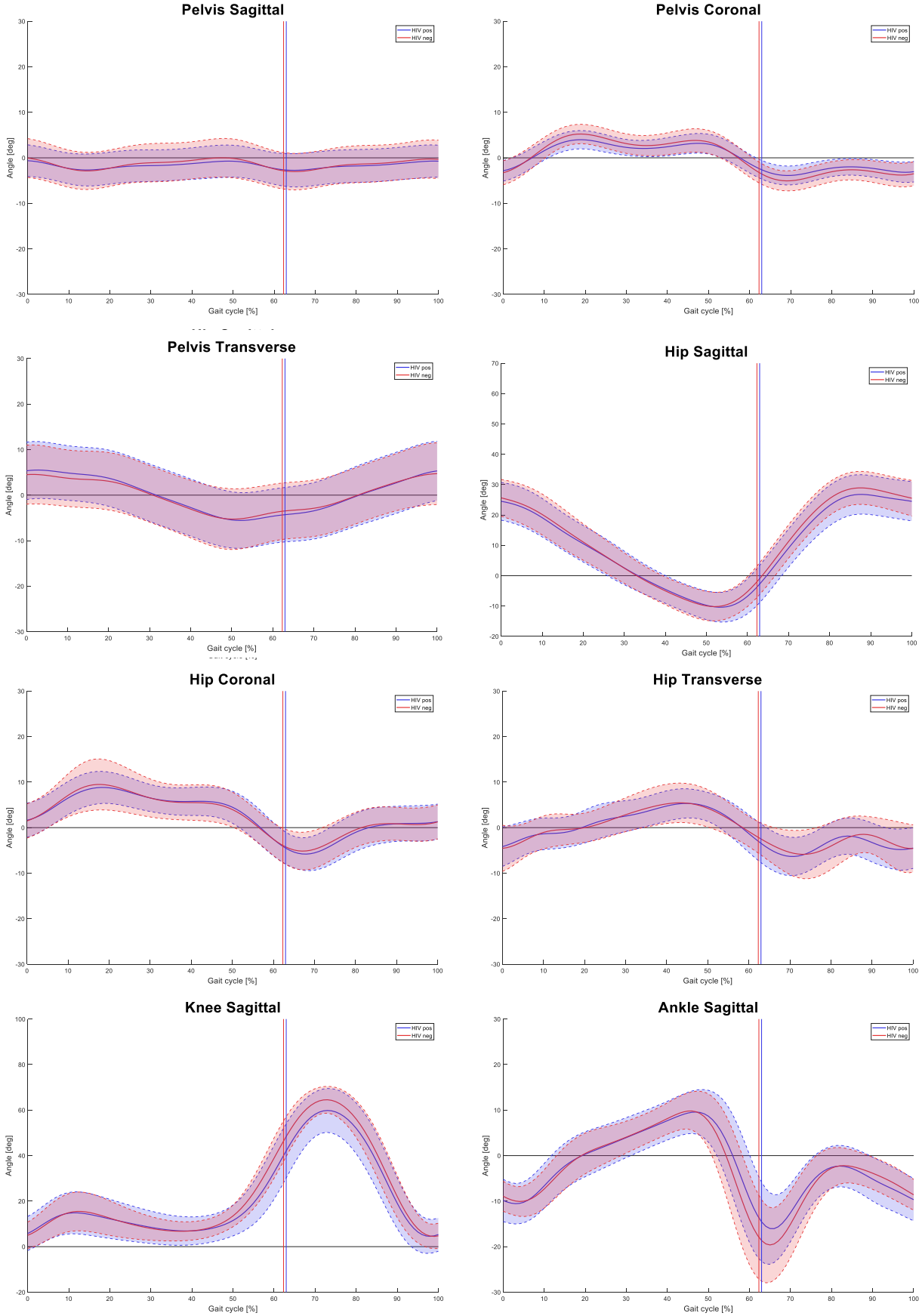

Figure 8.7. Kinematic gait curves for PLHIV (blue) and SNP (red) under dual task conditions. Solid curve lines indicate mean angular values and shaded areas bound by dashed lines indicate the respective standard deviations. vertical lines indicate toe-off. note that these graphs depict data that have not been adjusted for speed or other covariables.

Table 8.16. Kinematic lower limb angles and ROM during dual task gait in PLHIV and SNP. Blue arrows indicate the directional trend of the difference in PLHIV relative to SNP.

Group	n	Unadjusted			Adjusted		
		Mean ± SD (95% CI)	Difference (95% CI)	Unadjusted *p*-value	Mean ± SE (95% CI)	Difference (95% CI)	*p*-value
Pelvis tilt ROM during GC (°)							
PLHIV	39	4.4 (2.0)[#] (3.5; 5.5)	-0.6 (-1.4; 0.1)	0.124↓	5.2 ± 0.4 (4.5; 5.0)	0.1 ± 0.5 (-0.9; 1.1)	0.819=
SNP	47	4.8 (3.3)[#] (3.8; 7.2)			5.09 ± 0.4 (4.4; 5.8)		
Peak pelvis anterior tilt during GC (°)							
PLHIV	39	0.9 ± 3.5 (-0.2; 2.0)	-0.6 ± 0.8 (-2.3; 1.1)	0.469↓	0.9 ± 0.6 (-0.4; 2.1)	0.7 ± 0.9 (-1.1; 2.5)	0.462↑
SNP	47	1.5 ± 4.1 (0.3; 2.7)			0.2 ± 0.6 (-1.0; 1.5)		
Pelvis obliquity ROM during GC (°)							
PLHIV	39	9.3 ± 2.7 (8.4; 10.1)	-2.3 ± 0.6 (-3.5; 1.2)	**<0.001**↓	10.0 ± 0.4 (9.2; 10.9)	-0.5 ± 0.6 (-1.7; 0.7)	0.399↓
SNP	47	11.6 ± 2.8 (10.8; 12.5)			10.6 ± 0.4 (9.7; 11.4)		
Pelvis rotation ROM during GC (°)							
PLHIV	39	12.7(5.4)[#] (10.5; 15.9)	-0.9 (-2.8; 1.0)	**0.001**↓	14.5 ± 0.8 (12.9; 16.1)	1.3 ± 1.2 (-1.1; 3.6)	0.280↑
SNP	47	13.9(6.9)[#] (10.9; 17.8)			13.2 ± 0.8 (11.7; 14.8)		

Pelvis rotation angle at initial contact (°)							
PLHIV	39	5.3 ± 2.7 (4.4; 6.2)	0.8 ± 0.7 (-0.5; 2.2)	0.225↑	5.5 ± 0.5 (4.4; 6.6)	1.8 ± 0.8 (0.3; 3.3)	**0.022**↑
SNP	47	4.5 ± 3.5 (3.4; 5.5)			3.7 ± 0.5 (2.7; 4.7)		
Hip flexion ROM during GC (°)							
PLHIV	39	38.7 ± 5.3 (37,0; 40.5)	-1.7 ± 1.1 (-3.9; 0.5)	0.120↓	40.4 ± 0.7 (39.0; 41.7)	2.4 ± 1.0 (0.5; 4.4)	**0.016**↑
SNP	47	40.5 ± 4.9 (39.0; 41.9)			37.9 ± 0.7 (36.5; 39.3)		
Hip flexion ROM during loading response (°)							
PLHIV	39	7.9 ± 2.7 (7.0; 8.8)	0.8 ± 0.6 (-0.3; 1.9)	0.169↑	6.9 ± 0.4 (6.0; 7.7)	-0.4 ± 0.6 (-1.6; 0.8)	0.470↓
SNP	47	7.1 ± 2.6 (6.3; 7.9)			7.3 ± 0.4 (6.4; 8.1)		
Hip flexion ROM pre-swing to initial swing (°)							
PLHIV	39	8.0 ± 2.1 (7.4; 8.7)	-0.1 ± 0.5 (-1.1; 0.9)	0.793↓	8.0 ± 0.4 (7.2; 8.9)	-0.0 ± 0.6 (-1.2; 1.1)	0.964=
SNP	47	8.2 ± 2.4 (7.5; 8.9)			8.1 ± 0.4 (7.3; 8.9)		
Hip flexion angle at initial contact (°)							
PLHIV	39	24.6 ± 5.8 (22.7; 26.5)	-0.7 ± 1.3 (-1.8; 3.3)	0.341↓	25.5 ± 0.8 (24.0; 27.0)	2.8 ± 1.1 (0.6; 4.9)	**0.012**↑
SNP	47	25.8 ± 5.7 (24.1; 27.5)			22.7 ± 0.7 (21.3; 24.2)		

Peak hip flexion during swing (°)							
PLHIV	39	27.5 ± 6.0 (25.5; 29.4)	-2.1 ± 1.2 (-4.4; 0.3)	0.083↓	28.5 ± 0.8 (27.0; 30.0)		0.057↑
SNP	47	30.0 ± 5.0 (28.1; 31.0)			26.5 ± 0.7 (25.1; 28.0)		
Peak hip extension during stance (°)							
PLHIV	39	11.1 ± 4.6 (9.6; 12.6)	0.4 ± 1.0 (-1.5; 2.4)	0.670↑	12.1 ± 0.7 (10.6; 13.5)	0.6 ± 1.0 (-1.5; 2.7)	0.568↑
SNP	47	10.7 ± 4.4 (9.4; 12.0)			11.5 ± 0.7 (10.0; 12.9)		
Hip abduction ROM during mid-stance (°)							
PLHIV	39	4.2 ± 2.0 (3.5; 4.8)	-0.6 ± 0.4 (-1.5; 0.2)	0.148↓	4.9 ± 0.3 (4.3; 5.5)	0.7 ± 0.4 (-0.1; 1.5)	0.104↑
SNP	47	4.8 ± 2.1 (4.2; 5.4)			4.2 ± 0.3 (3.6; 4.8)		
Hip adduction ROM during loading response (°)							
PLHIV	39	6.1 ± 2.2 (5.4; 6.8)	-1.42 ± 0.5 (-2.4; 0.4)	**0.005**↓	6.3 ± 0.4 (5.6; 7.0)	-0.4 ± 0.5 (-1.4; 0.7)	0.460↓
SNP	47	7.5 ± 2.4 (6.8; 8.2)			6.7 ± 0.4 (6.0; 7.4)		
Hip internal rotation ROM during GC (°)							
PLHIV	39	16.1 ± 4.3 (14.7; 17.5)	0.9 ± 1.0 (-2.9; 1.1)	0.371↓	16.8 ± 0.8 (15.2; 18.4)	-0.0 ± 1.2 (-2.3; 2.3)	0.979=
SNP	47	17.0 ± 4.9 (15.6; 18.4)			16.8 ± 0.8 (15.2;18.4)		

Knee flexion ROM during GC (°)							
PLHIV	39	59.0(6.4)[#] (55.3; 61.7)	-4.6 (-6.5; 2.7)	**<0.001**↓	60.1 ± 0.9 (58.4; 61.8)	-2.9 ± 1.1 (-5.1; -0.6)	**0.013**↓
SNP	47	63.2 (6.1)[#] (60.8; 66.9)			63.0 ± 0.8 (61.4; 64.6)		
Knee flexion ROM during stance (°)							
PLHIV	39	10.1 (5.9)[#] (6.3; 12.2)	-1.6 (-3.3; 0.4)	0.130↓	11.7 ± 0.6 (10.5; 13.0)	0.8 ± .9 (1.1; 2.6)	0.411↑
SNP	47	11.0 (5.1)[#] (8.8; 13.9)			11.0 ± 0.6 (9.7; 12.2)		
Knee flexion ROM from stance to swing (°)							
PLHIV	39	54.8 (7.0)[#] (52.5; 59.5)	-4.8 (-6.6; 2.9)	**<0.001**↓	56.7 ± 0.9 (55.0; 58.5)	-2.3 ± 1.2 (-4.6; 0.0)	0.052↓
SNP	47	59.5 (5.4)[#] (57.5; 62.9)			59.0 ± 0.8 (57.4; 60.2)		
Knee extension ROM from mid-stance to terminal stance (°)							
PLHIV	39	9.0 ± 5.1 (7.4; 10.7)	-1.2 ± 1.2 (-3.5; 1.2)	0.318↓	11.4 ± 0.7 (9.9; 12.8)	2.3 ± 1.0 (0.3; 4.4)	**0.027**↑
SNP	47	10.2 ± 5.7 (8.5; 11.9)			9.1 ± 0.7 (7.7; 10.4)		
Knee flexion at initial contact (°)							
PLHIV	39	5.2 (10.5)[#] (0.8; 11.3)	0.8 (-2.0; 3.7)	0.529↑	6.4 ± 1.0 (4.5; 8.3)	3.7 ± 1.4 (1.0; .6.5)	**0.008**↑
SNP	47	4.3 (6.5)[#] (1.4; 7.8)			2.7 ± 0.9 (0.8; 4.6)		

Peak knee flexion during stance (°)							
PLHIV	38	42.1 ± 8.1 (39.5; 44.7)	-3.7 ± 1.4 (-6.5; 0.9)	**0.010**↓	44.3 ± 1.1 (42.1; 46.5)	0.1 ± 1.4 (-2.8; 3.0)	0.944=
SNP	47	45.8 ± 4.8 (44.4; 47.3)			44.2 ± 1.0 (42.2; 46.3)		
Peak knee extension during stance (°)							
PLHIV	38	-3.2 (7.9)# (-7.9; 0.0)	-0.7 (-3.3; 1.8)	0.490↑	-4.5 ± 0.8 (-6.2; -2.9)	-3.2 ± 1.2 (-5.5; -0.9)	**0.007**↑
SNP	47	-3.1 (5.0)# (-4.9; 0.0)			-1.3 ± 0.8 (-2.9; 0.3)		
Peak knee flexion during swing (°)							
PLHIV	38	60.9 ± 5.1 (58.1; 67.7)	-4.6 ± 1.5 (-7.6; -1.7)	**0.002**↓	63.5 ± 1.1 (61.4; 65.6)	0.1 ± 1.4 (-2.7; 2.9)	0.939=
SNP	47	65.6 ± 5.1 (64.1; 67.0)			63.3 ± 1.0 (61.4; 65.3)		
Ankle dorsiflexion ROM during stance (°)							
PLHIV	38	21.9 ± 3.6 (20.7; 23.1)	0.2 ± 0.8 (-1.3; 1.8)	0.756↓	20.9 ± 0.6 (19.8; 22.1)	-1.1 ± 0.8 (-2.8; 0.50)	0.171↓
SNP	47	21.6 ± 3.5 (20.6; 22.7)			22.1 ± 0.6 (21.0; 23.2)		
Ankle dorsiflexion ROM during swing (°)							
PLHIV	38	16.7 ± 4.8 (15.1; 18.2)	-3.2 ± 1.2 (-5.6; 0.8)	**0.008**↓	17.5 ± 1.0 (15.6; 19.4)	-1.4 ± 1.4 (-4.1; 1.4)	0.321↓
SNP	47	19.9 ± 6.0 (18.1; 21.6)			18.9 ± 0.9 (17.0; 20.8)		

Ankle plantarflexion ROM, heel rise to toe-off (push off) (°)							
PLHIV	38	27.4 (8.2)[#] (24.7; 32.9)	-3.9 (-6.5; 1.3)	**0.003**↓	29.2 ± 1.0 (27.2; 31.1)	-1.9 ± 1.4 (-4.6; 0.9)	0.182↓
SNP	47	31.7 (9.2)[#] (27.4; 36.6)			31.0 ± 0.9 (29.2; 32.9)		
Ankle dorsiflexion angle at initial contact (°)							
PLHIV	38	-9.3 (6.3)[#] (-12.2; -5.9)	-0.8 (-2.3; 0.8)	0.296↑	-9.1 ± 0.6 (-10.2; -7.0)	0.8 ± 0.8 (-0.8; 2.5)	0.307↓
SNP	47	-8.3 (3.6) (-10.6; -7.0)			-10.0 ± 0.6 (-11.1; -8.9)		
Ankle plantarflexion angle at toe-off (°)							
PLHIV	38	15.5 ± 6.3 (13.4; 20.5)	-3.1 ± 1.4 (-5.8; 0.4)	**0.025**↓	16.8 ± 1.1 (14.7; 19.0)	-0.8 ± 1.6 (-3.9; 2.2)	0.585↓
SNP	47	18.6 ± 6.3 (16.8; 20.5)			17.7 ± 1.1 (15.6; 19.8)		
Peak ankle plantarflexion during GC (°)							
PLHIV	38	18.8 (6.8)[#] (14.1; 20.9)	-3.3 (-6.2; 0.3)	**0.035**↓	19.5 ± 1.1 (17.3; 21.7)	-1.9 ± 1.6 (-5.0; 1.2)	0.233↓
SNP	47	21.8 (10.6)[#] (16.8; 27.4)			21.3 ± 1.1 (19.2; 23.5)		

Abbreviations: CI = confidence interval; GC = gait cycle; n = number of participants; PLHIV = people living with HIV-1 infection; ROM = range of motion; SD = standard deviation; SE = standard error; SNP = HIV-seronegative participants.
Covariables were gender (male/female), age (in years) and normalised gait speed.
[#]presented as median (IQR) (Q1; Q3).

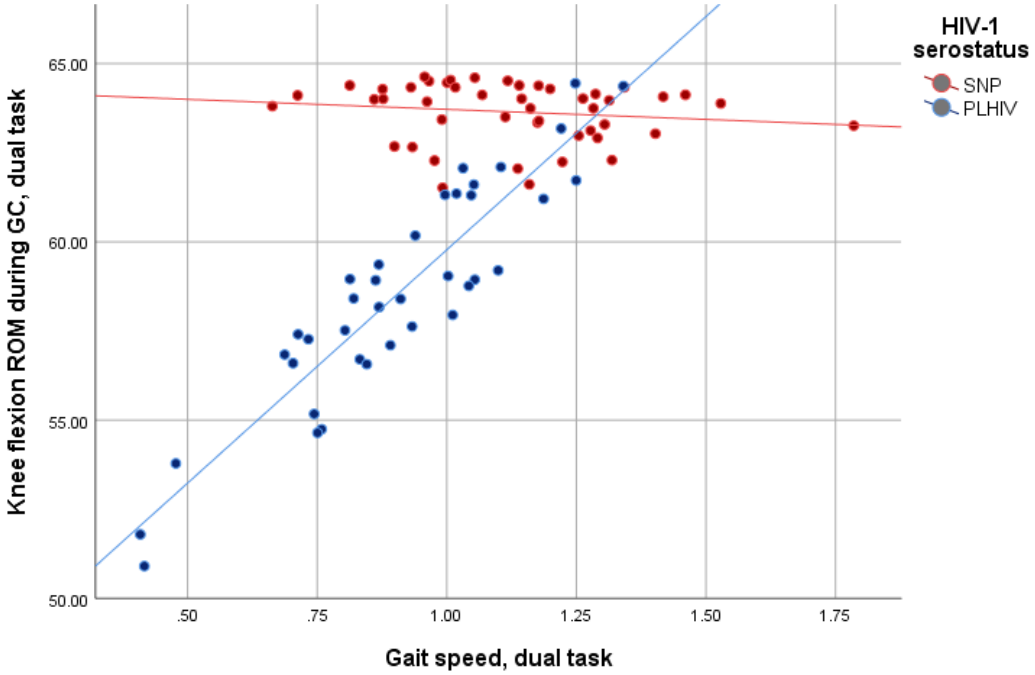

Figure 8.8. The interaction noted between HIV-serostatus and gait speed on knee flexion range during the gait cycle. Under dual task conditions, the effect of HIV on reducing knee flexion range during the gait cycle depends on the walking speed and appears larger at slower speeds.

8.6. Differences in biomechanical standing balance outcomes

8.6.1. Centre of pressure (COP) parameters during dual task single leg stance

COP data were only analysed for the dual task condition for the purposes of this thesis, given that only 22 SNP and seven PLHIV were able to complete the full 30-second trial with eyes closed. Shorter time intervals from this condition will be analysed at a later stage, but for the purposes of this dissertation it was decided to present the zero to 30 second time interval (full trial data) as this would provide the most reliable data for COP outcomes[390,466] and would enable comparison to previous studies performed in PLHIV.[62,323]

SLS DT data were available for 45 SNP and 40 PLHIV (i.e. 85% of the total sample). Since DT activities were only introduced later in the protocol, no such data were collected for 12 study participants (n = 3 SNP and n = 6 PLHIV). In addition, one SNP had invalid SLS DT trials due to constant foot shuffling, two PLHIV had invalid trials due to shuffling and one PLHIV was unable to perform SLS under the dual task condition (unsafe). A single best trial per participant was selected for analysis since few participants had two or three successful full-length trials (this is also how the SLS test is often used in clinical practice).[467]

Table 8.17 presents the COP results (unadjusted and adjusted for gender differences). The data for mean COP velocity in the ML direction (p = 0.031) and mean COP excursion in the ML direction (p = 0.08) whilst performing a dual task demonstrated significant differences between PLHIV and SNP. Mean velocity was increased in PLHIV, indicating that this group displayed faster COP movement in the ML direction, or needed more postural adjustments to maintain stability compared to SNP. Significantly larger excursion in the ML direction was also evident for PLHIV. No significant differences in COP AP or combined parameters were found between the groups.

After adjusting for gender, differences in mean COP excursion in ML direction remained significant, but the difference noted for mean ML velocity became non-significant and mean COP combined instead became significant (p = 0.027).

When performing adjusted analyses, mean COP excursion demonstrated a significant Levene's test (p = 0.038) and further checking of assumptions demonstrated skewed distribution of the residuals (Shapiro Wilk test = 0,025 and 0.035 for SNP and PLHIV

respectively). After inspecting the stabilogram and video data, the participant was deemed to be a true outlier, who demonstrated large movements whilst maintaining SLS. Sensitivity analyses were performed to assess the impact of removing the outlier. Removal of the outlier led to an insignificant Levene's test (p = 620) and normal distribution of the residuals (Shapiro Wilk = 0.232 and 0.320 for SNP and PLHIV respectively); however, the conclusions drawn from the adjusted analysis did not change as the difference between groups remained non-significant (mean difference = 0.71 mm ± 0.54 mm, p = 0.197, 95% CI = -0.38 mm to 1.79 mm. Therefore, the outlier was retained in the analysis.

Table 8.17. Centre of pressure (COP) outcomes for dual task single leg standing in PLHIV and SNP.

Group	n	Unadjusted			Adjusted		
		Estimate	Difference (95% CI)	*p*-value	mean ± SE (95% CI)	Difference (95% CI)	*p*-value[+]
Mean COP velocity (mm/s) (0 –30s)							
PLHIV	34	44.55 (23.98) (36.46; 60.44)	5.41 (-0.76; 12.36)	0.071[#↑]	51.17 ± 2.85 (45.48; 56.85)	7.68 ± 4.48 (-1.25;16.61)	0.091[↑]
SNP	38	39.23 (16.70) (33.65; 50.33)			43.49 ± 3.45 (36.60; 50.38)		
Mean COP velocity (mm/s) in AP direction (0 – 30s)							
PLHIV	34	25.09 (12.30) ()	2.35 (-1.38; 6.36)	0.180[#↑]	29.22 ± 1.89 (25.44; 32.99)	4.61 ± 2.97 (-1.32; 10.54)	0.126[↑]
SNP	38	22.77 (9.28) (19.58; 28.86)			24.61 ± 2.29 (20.03; 29.18)		
Mean COP velocity (mm/s) in ML direction (0 – 30s)							
PLHIV	34	30.99 (17.43) (26.95; 44.38)	4.91 (0.32; 9.55)	**0.031**[#↑]	35.97 ± 1.85 (32.28; 39.67)	5.13 ± 2.91 (-0.67; 10.93)	0.082[↑]
SNP	38	27.75 (12.62) (22.60; 35.22)			30.84 ± 2.24 (26.37; 35.32)		

Mean COP excursion (mm) (0-30 s)							
PLHIV	34	9.63 ± 2.39 (8.79; 10.46)	1.01 ± 0.51 (0.00; 2.02)	0.050↑	9.71 ± 0.36	1.29 ± 0.57 (0.16; 2.43)	**0.027**↑
SNP	38	8.62 ± 1.89 (7.99; 9.24)			8.42 ± 0.44		
Mean COP distance (mm) in AP direction (0 – 30s)							
PLHIV	34	6.23 ± 1.90 (5.57; 6.89)	0.42 ± 0.41 (-0.40; 1.25)	0.312$↑	6.28 ± 0.30 (5.68; 6.89)	0.66 ± 0.47 (-0.29; 1.60)	0.169↑
SNP	38	5.81 ± 1.62 (5.27; 6.34)			5.63 ± 0.37 (4.90 6.35)		
Mean COP distance (mm) in ML direction (0 – 30s)							
PLHIV	34	6.06 ± 1.54 (5.52; 6.59)	0.85 ± 0.31 (0.23; 1.47)	**0.008**$↑	6.11 ± 0.22 (5.67; 6.56)	0.95 ± 0.35 (0.25; 1.65)	**0.008**↑
SNP	38	5.21 ± 1.07 (4.85; 5.56)			5.16 ± 0.27 (4.62; 5.70)		

Abbreviations: AP = anterior-posterior direction; CI = confidence interval; COP = centre of pressure; GC = gait cycle; n = number of participants; ML = medial-lateral direction; PLHIV = people living with HIV-1 infection; ROM = range of motion; SD = standard deviation; SE = standard error; SNP = HIV-seronegative participants.
The adjusted model included gender.
[a]*presented as median (IQR) (Q1 – Q3) or mean ± SD (95% CI).*
[#]*Mann-Whitney U test.*
[$]*Independent student's t-test.*
[+]*F-test from 2x2 ANOVA (HIV-serostatus x gender).*

8.7. Correlations of clinical tests with a complex and quantitative composite gait score, self-reported function and fall-related outcomes in PLHIV

Table 8.18 below presents (for PLHIV only) the correlation matrix of the selected clinical tests with a quantitative summary measure of gait (the EGVI), self-reported function and fall history, with associations being reported as either Pearson product-moment (r) or Spearman's rank (r_s) correlation coefficients. Cells with significant correlations ($\rho < 0.05$) are highlighted in orange (darker orange denotes the corresponding r-value of the significant correlation, with the *p*-value highlighted in lighter orange). Refer to Section 7.10.3 for interpretation of strength of correlation coefficients.

Table 8.18. Pearson product moment (indicated with §) and Spearman's rank correlation coefficients showing relationships between the EGVI, self-reported function and fall number with clinical measures of mobility. Highlighted cells indicate significant correlations (dark and light orange for correlation coefficient and *p*-value respectively).

PLHIV (58% female; median age 36.61 years)		EGVI. usual-paced	EGVI. dual task	Self-reported function: Mobility	Self-reported function: Self-care	Self-reported function: Usual activities	Number of falls over past year
PPB total ratio score (0 - 4)	Correlation Coefficient	0.30	**0.37**	**-0.46**	**-0.44**	**-0.41**	0.02
	Sig. (2-tailed)	0.058	**0.032**	**0.001**	**0.002**	**0.003**	0.888
	n	42	33	49	49	49	50
PPB balance ratio score	Correlation Coefficient	0.05	-0.28	**-0.34**	**-0.30**	-0.14	**-0.45**
	Sig. (2-tailed)	0.746	0.112	**0.018**	**0.037**	0.356	**0.001**
	n	42	33	49	49	49	50
PPB usual walk ratio score	Correlation Coefficient	0.17§	0.25§	**-0.51**	**-0.41**	**-0.39**	0.11
	Sig. (2-tailed)	0.276	0.167	**0.000**	**0.003**	**0.006**	0.432
	n	42	33	49	49	49	50
PPB narrow walk ratio score	Correlation Coefficient	0.22§	0.10§	**-0.39**	**-0.37**	**-0.41**	0.20
	Sig. (2-tailed)	0.155	0.583	**0.005**	**0.008**	**0.004**	0.155
	n	42	33	49	49	49	50
PPB chair rise ratio score	Correlation Coefficient	**0.36§**	**0.42§**	**-0.44**	**-0.48**	**-0.29**	-0.16
	Sig. (2-tailed)	**0.021**	**0.016**	**0.001**	**<0.001**	**0.042**	0.270
	n	42	33	49	49	49	50
Six-metre Walk Test (time in seconds converted to speed)	Correlation Coefficient	0.17§	0.25§	**-0.51**	**-0.41**	**-0.39**	0.11
	Sig. (2-tailed)	0.276	0.167	**<0.001**	**0.003**	**0.006**	0.432
	n	42	33	49	49	49	50
Six-metre Walk Test, dual task (time in seconds converted to speed)	Correlation Coefficient	0.25§	0.30§	**-0.36**	-0.14	-0.23	-0.11
	Sig. (2-tailed)	0.160	0.090	**0.024**	0.386	0.161	0.514
	n	33	33	40	40	40	41
Five-Times STS test	Correlation Coefficient	**-0.36§**	**-0.42§**	**0.44**	**0.48**	**0.29**	0.16

(time in seconds)	Sig. (2-tailed)	**0.019**	**0.016**	**0.001**	**<0.001**	**0.042**	0.270
	n	42	33	49	49	49	50
30-second STS test (repetitions completed)	Correlation Coefficient	**0.35**[§]	**0.37**[§]	**-0.36**	**-0.46**	**-0.38**	-0.13
	Sig. (2-tailed)	**0.021**	**0.033**	**0.010**	**0.001**	**0.008**	0.364
	n	42	33	49	49	49	50
Single Leg Stance Test, eyes closed (time in seconds)	Correlation Coefficient	0.22	-0.06	**-0.46**	**-0.46**	**-0.30**	-0.19
	Sig. (2-tailed)	0.169	0.732	**0.001**	**0.001**	**0.039**	0.184
	n	42	33	49	49	49	50
Single Leg Stance Test, dual task (time in seconds)	Correlation Coefficient	-0.06	-0.26	0.00	-0.11	-0.30	-0.24
	Sig. (2-tailed)	0.752	0.150	0.985	0.509	0.064	0.133
	n	33	33	40	40	40	41

Abbreviations: n = number of participants; PLHIV = people living with HIV-1 infection; PPB = Health ABC Physical Performance Battery; Sig. = Statistical significance; STS = Sit-To-Stand.
Bold print indicates statistically significant correlations (p < 0.05) regardless of strength of correlation..
Correlations of 0.2 ≤ 0.39 = weak; 0.4 ≤ 0.59 = moderate; 0.6 ≤ 0.79 = strong; 0.8 ≤ 1.0 = very strong.[462]

Figures 8.9 to 8.13 are scatterplot graphs of selected significant correlations as reported in Table 8.18 above. Associations between clinical tests and the EGVI and fall history are shown, as well as the test showing the best correlation with self-reported function (since most clinical tests demonstrated significant correlations with self-reported function). All correlations were moderate to weak.

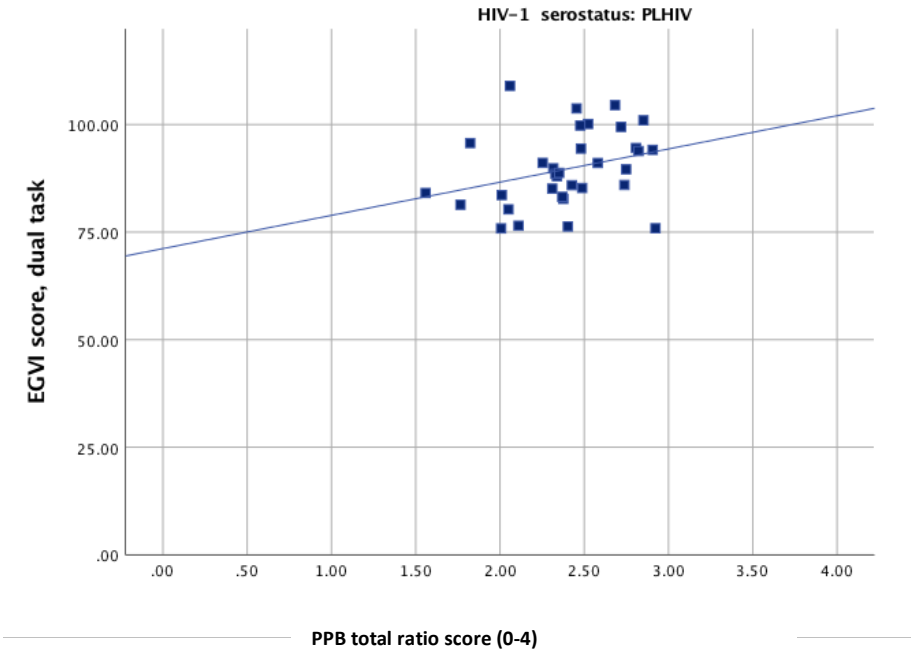

Figure 8.9. The positive correlation between PPB total score and the EGVI calculated for the dual task condition in PLHIV (r_s = 0.37).

Figure 8.9 above shows that PLHIV who achieved higher (better) total scores on the PPB also demonstrated higher EGVI scores under the dual task condition (i.e. gait pattern variability closer to the norm, represented by a score of 100).

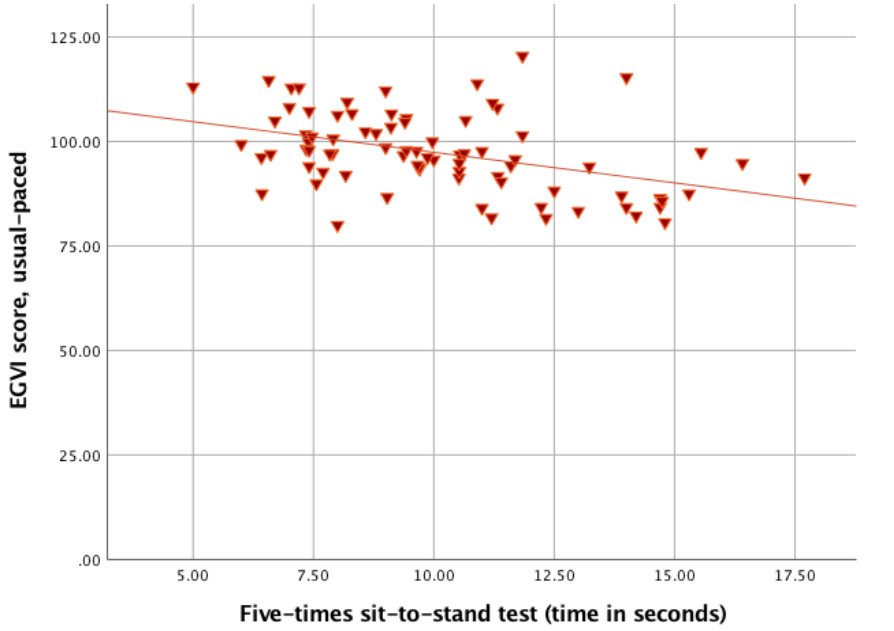

Figure 8.10. The negative correlation between the Five-Times Sit-To-Stand Test (time in seconds) and the EGVI calculated for usual-paced gait in PLHIV (r = -0.36).

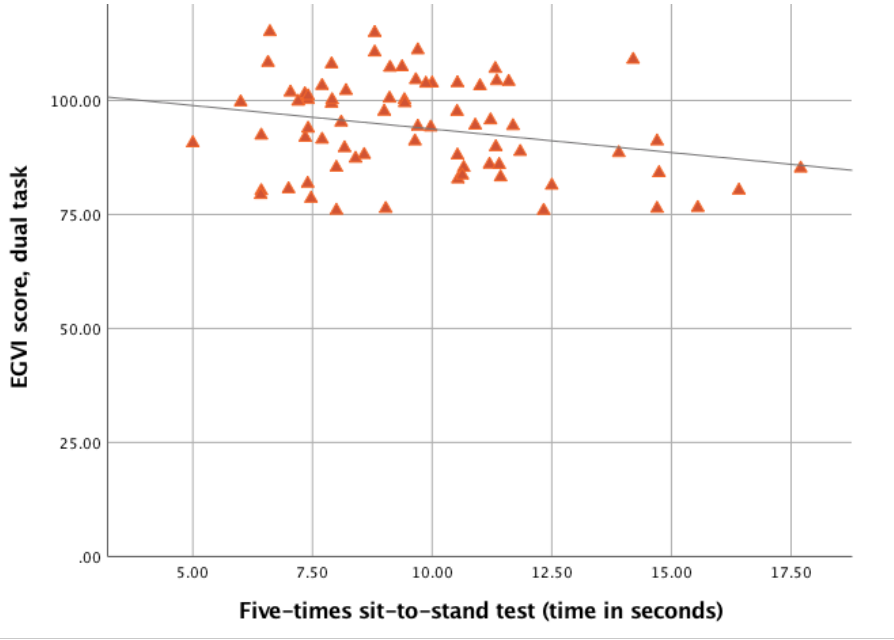

Figure 8.11. The negative correlation between the Five-Times Sit-To-Stand Test (time in seconds) and the EGVI calculated for dual task gait in PLHIV (r = -0.42).

The 5STS test (time in seconds) correlated the best with EGVI scores, although the correlations were weak for EGVI scores calculated for usual-paced gait, and only moderate for scores calculated for dual task gait. Figure 8.10 (previous page) and Figure 8.11 above show that PLHIV took a longer time to complete five repeated sit-to-stand actions and also demonstrated lower EGVI scores for usual-paced gait as well as dual task gait (i.e. lower gait variability than the norm).

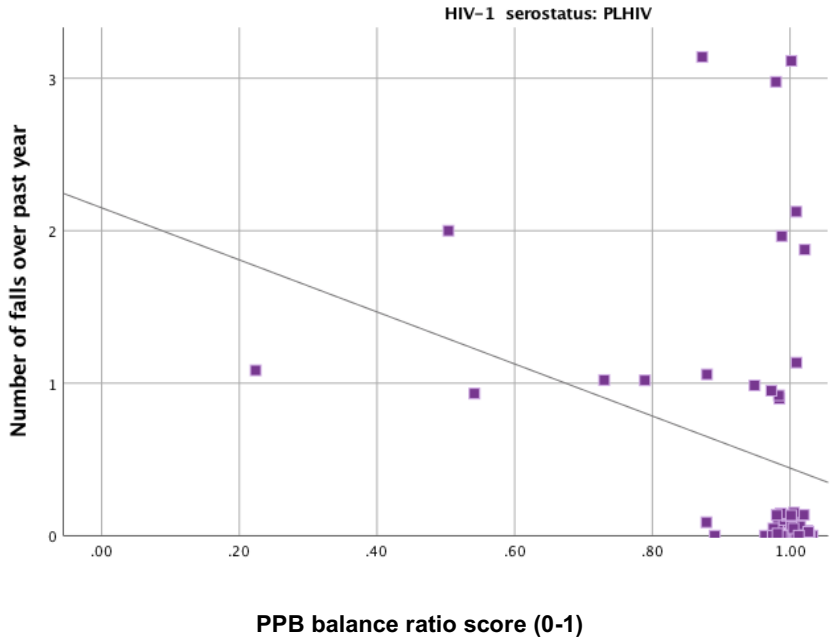

Figure 8.12. The negative correlation between the PPB balance ratio score (maximum score of 1) and number of falls during the past 12 months (r_S = -0.45). Note that a jitter function was applied to the nominal data in the plot to enhance graphic representation of the correlation.

Figure 8.12 above shows that PLHIV achieving maximum scores on the balance sub score of the PPB (maximum ratio score of 1, based on semi-tandem, full-tandem and single leg stance tests of 30 seconds each) were most likely not to have reported any falls over the past 12 months. However, some of those achieving maximum scores also reported one or more falls – this is explained by the fact that this test demonstrated a very high ceiling effect in PLHIV (Table 8.7) and is thus likely too easy a test to discriminate fallers from non-fallers.

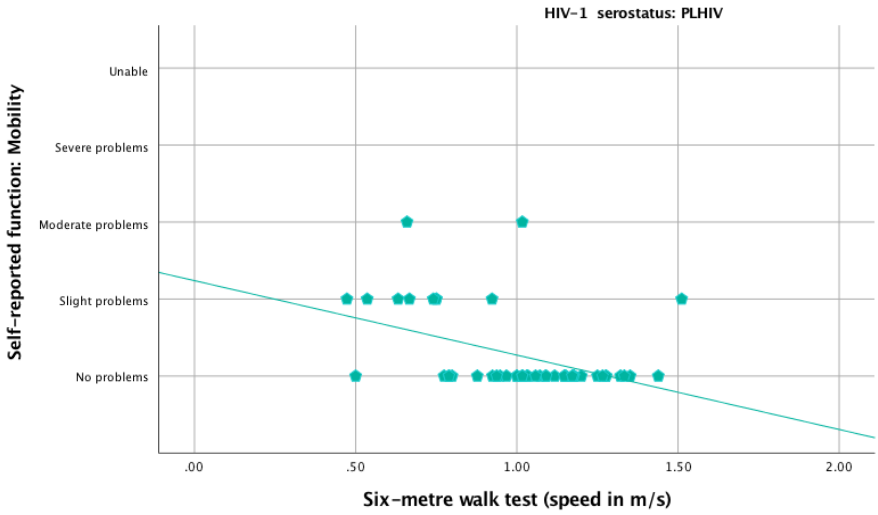

Figure 8.13. The negative correlation between Six-metre Walk Test performance (time in seconds converted to walking speed) and self-reported mobility function, where a lower EQ-5D-5L score indicates better function (r_S = -0.51).

Figure 8.13 above shows that PLHIV who were faster in completing the 6mWT tended to report higher mobility function (i.e. a lower EQ-5D-5L score, or less problems with walking).

Associations between the selected clinical tests and the binary variables (yes/no) of having experienced any fall over the past year, as well as having a fear of falling, were assessed using independent Student's t-test or Mann-Whitney U tests, depending on the data distribution. PLHIV reporting a fear of falling achieved significantly worse scores in the total PPB, the PPB narrow walk sub score and the PPB chair rise sub score. Those with a fear of falling also performed significantly worse in the SLS EC, required a significantly longer time to complete 5STS actions, and completed significantly less STS repetitions within 30-seconds (Table 8.19).

Table 8.19. Comparisons of clinical test performance in PLHIV with and without fear of falling. Orange cells (dark or light) indicate significant *p*-values.

PLHIV (58% female; median age 36.61 years)	Fear of falling (n = 10)	No fear of falling (n = 40)	*p*-value
PPB total ratio score (0 - 4)	2.28 (1.53; 2.37)	2.49 (2.34; 2.75)	**0.008**
PPB balance ratio score	0.99 (0.68; 1.00)	1.00 (1.00; 1.00)	0.092
PPB usual walk ratio score	0.47 ± 0.15	0.52 ± 0.11	0.248
PPB narrow walk ratio score	0.42 ± 0.16	0.52 ± 0.13	**0.048**
PPB chair rise ratio score	0.37 ± 0.07	0.48 ± 0.12	**0.008**
Six-metre Walk Test (time in seconds converted to speed)	0.93 ± 0.30	1.03 ± 0.23	0.248
Six-metre Walk Test, dual task (time in seconds converted to speed)	0.67 ± 0.23	0.78 ± 0.28	0.278
Five-Times STS test (time in seconds)	13.93 ± 2.69	11.00 ± 2.57	**0.003**
30-second STS Test (repetitions completed)	12.70 ± 4.40	16.75 ± 4.87	**0.021**
Single Leg Stance Test, eyes closed (time in seconds)	4.18 (0.00; 7.94)	9.14 (5.64; 17.90)	**0.004**

Single Leg Stance Test, dual task (time in seconds)	23.50 (13.38; 30.00)	30.00 (25.30; 30.00)	0.112

Abbreviations: n = number of participants; PLHIV = people living with HIV-1 infection; PPB = Health ABC Physical Performance Battery; Q1 = first quartile; Q3 = third quartile; SD = standard deviation; STS = Sit-To-Stand;
Results are presented as median (Q1; Q3) or mean ± SD. p-values obtained from independent Student's t-tests or Mann-Whitney U tests.
Bold print (in orange cells) indicates statistical significance, $p < 0.05$.

The PPB balance sub score was the only clinical test to show a significant difference between PLHIV with a retrospective self-report of experiencing any falls during the past year and those with no fall history. Those reporting previous falls achieved a significantly lower ratio score in this domain of the PPB (Table 8.20).

Table 8.20. Comparisons of clinical test performance in PLHIV with and without any falls during the past year. Orange cells indicate significant *p*-values.

PLHIV (58% female; median age 36.61 years)	**Any fall during past year (n = 17)**	**No falls during past year (n = 33)**	***p*-value**
PPB total ratio score (0 - 4)	2.40 (1.73; 2.68)	2.45 (2.21; 2.74)	0.927
PPB balance ratio score	0.96 (0.76; 1.00)	1.00 (1.00; 1.00)	**<0.001**
PPB usual walk ratio score	0.53 ± 0.15	0.50 ± 0.11	0.434
PPB narrow walk ratio score	0.53 ± 0.16	0.42 ± 0.12	0.299
PPB chair rise ratio score	0.44 ± 0.12	0.47 ± 0.12	0.340
Six-metre Walk Test (time in seconds converted to speed)	1.05 ± 0.29	0.99 ± 0.22	0.434
Six-metre Walk Test, dual task (time in seconds converted to speed)	0.71 ± 0.28	0.77 ± 0.27	0.494
Five-Times STS Test (time in seconds)	12.28 ± 3.23	11.24 ± 2.58	0.222
30-second STS Test (repetitions completed)	15.35 ± 6.16	16.24 ± 4.37	0.557

Single Leg Stance Test, eyes closed (time in seconds)	5.45 (0.25; 8.75)	9.1 (4.92; 17.45)	0.091
Single Leg Stance Test, dual task (time in seconds)	25.00 (17.15; 30.00)	30.00 (26.65; 30.00)	0.094

Abbreviations: n = number of participants; PLHIV = people living with HIV-1 infection; PPB = Health ABC Physical Performance Battery; Q1 = first quartile; Q3 = third quartile; SD = standard deviation; STS = Sit-To-Stand;
Results are presented as median (Q1; Q3) or mean ± SD. p-values obtained from independent Student's t-tests or Mann-Whitney U tests.
Bold print (orange cells) indicates statistical significance, $p < 0.05$.

8.8. Chapter summary

This chapter presented the results of the cross-sectional field study. The two participant groups (PLHIV and SNP) differed with regards to median age (although both groups were on average in their thirties) and gender composition (both groups were predominantly female, but SNP included a significantly higher percentage of women).

Instrumented gait analysis showed that PLHIV walked significantly slower than SNP under all task conditions (although for fast-paced gait, this difference disappeared in adjusted analysis). Unadjusted comparisons of TSPs showed differences typically associated with a slow gait speed. After adjusting for covariables including speed, differences were less and mostly remained for temporal and temporospatial parameters, but not spatial or temporophasic parameters. Kinematic angles during gait were mostly reduced in PLHIV, as would be expected from the TSP results. After adjusting for covariables, dual task gait showed the most differences, with increased proximal angles (hip and knee), except for knee flexion range during the gait cycle, which was significantly decreased in PLHIV. No significant differences were evident at the ankle, although all ankle angles and ranges demonstrated trends towards being decreased in PLHIV. EGVI scores revealed significantly lower scores in PLHIV for usual-paced as well as dual task gait. These results remained after adjusted analyses and demonstrate lower gait variability in PLHIV relative to what is consider the norm (in SNP). PLHIV demonstrated increased COP balance measures in the ML direction, and, after adjustment for gender, for total COP excursion.

Relative to SNP, PLHIV reported significantly lower mobility and selfcare function. Clinical test performance revealed that PLHIV were significantly impaired on clinical tests relative to their

seronegative peers, even after adjusting for covariables, although some ceiling effects were noted especially for static balance tests.

All clinical tests (except SLS DT) showed moderate to weak correlations with the domains of self-reported function. Only the balance sub score of the PPB correlated significantly with fall history, but this test component may be of limited utility in PLHIV. The chair rise tests, and in particular the 5STS test, correlated the best with quantitative EGVI scores and also with self-reported function (albeit still all moderate to weak correlations). This test also demonstrated a significant association with fear of falling in PLHIV.

These findings, in the context of Parts I and II of the dissertation, and relevant implications, will subsequently be discussed in Chapter 9, the general Discussion of the dissertation.

CHAPTER 9
DISCUSSION

9.1. Introduction

This project provided novel quantitative information about locomotor impairments found among people living with HIV-1 infection (PLHIV) residing in the Cape Winelands District of the Western Cape, South Africa, using state-of-the-art three-dimensional (3D) movement analysis technology. The study further correlated the findings of 3D gait analysis (3DGA), as well as self-reported function and history and fear of falling, to selected physical performance tests which may be considered in clinical settings to screen for early functional decline in PLHIV.

9.1.1. Overview of the research presented in the dissertation

The dissertation was divided into three parts to present a systematic review and three primary studies*, viz:*

- **Part I** reviewed the chronic nature of HIV-1 and its consequences related to various body systems, including a published systematic review[62] of the current evidence related to objective locomotor impairments in PLHIV. Review results provided the theoretical groundwork for the study conceptualisation and aided in selecting clinically relevant gait and balance outcomes and clinical tests.
- **Part II** of the dissertation involved two related observational laboratory-based studies to test the validity and reliability of gait outcomes measured by a newly-acquired portable 3DGA system. Results from these studies informed the interpretation of gait differences noted between PLHIV and HIV-seronegative participants (SNP) in the cross-sectional field study.
- **Part III** presented the third and main observational study and incorporated the theoretical hypotheses derived from Part I along with the technical insights gained from Part II. The outcome of Part III was not only the description of key biomechanical differences in the gait and balance of PLHIV relative to SNP, but also the proposal of a valid physical performance test for early clinical screening which can be used in clinical practice.

Presented within a framework of the general effects of ageing on locomotor function, this chapter will provide an integrated discussion of the key findings from the various studies and contributions towards the understanding of gait and balance impairments in PLHIV, the rigour of such findings, the participant profile and potential implications for rehabilitation, and the use of a simple, standardised, valid clinical performance test in PLHIV.

9.2. Evidence for walking gait and balance impairments among South African adults living with HIV-1 infection

Chapter 3 presented a systematic overview of evidence supporting increased postural sway and velocity in PLHIV under challenging conditions, as quantitatively determined by static posturography. The review highlights that little quantitative data is available about walking gait in PLHIV. Furthermore, methodological differences complicate comparisons between studies or to data from HIV-seronegative cohorts, and the evidence is mostly of fair to low quality. However, the limited information (mostly described in high-income countries) suggested that gait and balance impairments exist in middle-aged PLHIV, resembling fall-associated metrics in the elderly.[62]

9.2.1. Gait speed

The cross-sectional data from this PhD provide new knowledge by showing that the gait of PLHIV is primarily characterised by a significant slowing of movement. This observation is based on comparisons to community-matched SNP, and was evident when walking at a usual pace or when counting backwards while walking (performing a dual task), even after adjusting for covariables. Comparing these results to findings from Chapter 3,[30,32,49,59,121,261] this study provides new information about the way walking speed impairments manifest in PLHIV. The systematic review (Chapter 3) established that PLHIV demonstrate slowed walking when having to produce a fast gait, but not when walking at a usual pace.[62] Notably, the methodologies of included studies assessing gait speed varied substantially, and most of the evidence was derived from studies measuring tests such as six-minute walking distance (6MWD).[2,3,55,59,121,260,261] Although proven to correlate well with gait speed,[299] 6MWD measures different aspects of walking function than short distance walking tests, since it is actually an indicator of functional aerobic capacity.[468] Furthermore, most of the studies reporting differences in 6MWD used predicted norms from the literature for comparison. This is of concern, as gait patterns strongly relate to – and is influenced by – the community or culture that a person hails from.[209] Therefore larger between-group differences may be apparent when

comparing data collected in patients from a certain population or community and a comparison group from another; for example when healthy people (and not just patients) from the same underlying population would tend to walk slower than healthy people in a different "normative" reference dataset (e.g. data from the general population, which may have been readily available from population-based studies, routine health information systems and registries).

The pitfalls of deriving inferences from inappropriate reference groups in HIV research are reported.[469] Conclusions regarding accelerated or accentuated ageing in PLHIV may for example merely reflect the underlying age distribution in the two cohorts being compared in studies failing to use appropriately matched comparison groups.[152] However, recruiting a matched comparison group in HIV research is by no means a trivial task,[152,469] as was evident during data collection for this study by failed efforts to recruit a sample matched on age and gender, despite the help of a research nurse. This issue was addressed by statistically adjusting comparisons of main outcomes for age, gender and selected important covariables associated with locomotor outcomes (e.g. gait speed) in this community-matched cohort to ascertain true between-group differences in locomotor characteristics.[469]

When trying to explain the slow gait speed noted among PLHIV in this study, various hypotheses may be considered. This study excluded people with peripheral neuropathy and therefore neuropathy or associated pain was not likely a reason for walking slower. After controlling for the effects of age, gender and speed, PLHIV walked with increased temporal parameters (absolute time spent in stance and producing steps), confirming the general slowness of movement and explaining the significantly slowed usual-paced gait speed. More insight was gained by considering adjusted analysis of dual task gait. This analysis adds additional insight because it shows biomechanical adaptations elicited under cognitive load and which are primarily attributable to disease physiology, without the confounding effects of speed, age or gender. PLHIV namely walked with an increased step time and had difficulty in generating sufficient stride lengths, resulting in the slower speed. These changes resemble a commonly-reported strategy in older adults to increase stability and reduce variability, specifically in the presence of fear of falling.[238,470] In this study, one-fifth of PLHIV reported suffering from a fear of falling (Table 8.6). It is feasible that this fear may have contributed in adopting an overly-controlled pattern in an effort to achieve a "safe" gait.

Even more relevant perhaps, is considering the three gait domains proposed by Verghese et al.[471] as being characteristic of gait performance in older adults at risk of cognitive decline and dementia. According to this theory, (i) changes in the rhythm domain (characterised by cadence, swing time and stance time) are associated with declines in memory, (ii) changes in

the pace domain (characterised by speed and stride length) relate to reduced executive function and (iii) changes in the variability domain (characterised by stride length variability) are associated with mild cognitive decline.[471] The changes noted under dual task conditions in PLHIV in this study thus fit the domains related to executive function and mild cognitive impairment. This is concurrent with reports that executive function is affected by HIV-1 infection[298] and that neurocognitive decline of varying severity occur in HIV[293,294,296,472] and has been associated with slow timed gait tests in this population.[473] Furthermore, as noted in Chapter 2, volumetric changes in the cerebellar white matter and subcortical grey matter of PLHIV – both of which are brain regions involved in motor control and cognition - may be associated with the development of mobility disability despite well-controlled viral load. Hinken et al.[186] previously used a dual task paradigm (using auditory reaction time and visual choice tasks) in PLHIV and demonstrated that HIV-1 infection is associated with impairments in divided attention and the simultaneous processing of competing stimuli, even in asymptomatic PLHIV. Such deficits have been associated with disruption of the anterior attentional system.[186] Gait speed is particularly sensitive to white matter alterations. The involvement of central motor and sensory systems similar to that seen with ageing may therefore be implicated in PLHIV, as has also been suggested by prior studies.[474]

Whether this slowing in speed and shortening of stride length successfully produced a safer gait is uncertain, considering that a third of PLHIV in this study experienced one or more falls during the past year (Table 8.6). Given the lower enhanced Gait Variability Index (EGVI) scores achieved in PLHIV versus SNP, which indicate reduced gait variability,[372] it seems that PLHIV succeeded in their efforts to implement a less variable gait. Walking with shorter steps maintains the centre of mass (COM) closer to the moving base of support (BOS) and should thus be more stable.[475] However, step length shortening may also be maladaptive,[476] and an over-controlled gait may thus be vulnerable to unexpected perturbations. It may thus be questioned whether the less variable gait pattern was truly the safer option – this is discussed further in Section 9.2.3.

9.2.2. Kinematic patterns

A key finding of this research project is that PLHIV showed changes in joint range of motion (ROM), especially at the hip and knee and in a distal-to-proximal pattern-shift in joint excursion. PLHIV had significantly increased hip ROM (similar finding to elderly gait)[232] and reduced knee ROM (similar finding to elderly gait, although this is an inconsistent observation in older adults)[232] whilst ankle plantarflexion was not significantly reduced during push-off (different to elderly gait).[232] The expectation that PLHIV might demonstrate a kinematic gait pattern similar

to that observed in elderly gait was thus partly confirmed under dual task conditions and independent of gait speed.

Albeit statistically significant, the magnitudes of these angular differences between PLHIV and SNP were not large (all smaller than 5° in Table 8.16, which is considered a general threshold for clinical significance in various adult populations).[318] On the other hand, the differences all exceeded 2°, the threshold generally considered in kinematic literature to distinguish artefacts of measurement error.[327,477] These angles also all exceeded the relevant measurement errors determined for each outcome using the myoMOTION system/model in Chapter 6 (except for the 2.3° increase in knee extension ROM noted for PLHIV; versus a standard error of measurement [SEM] of 2.4°). This implies that the differences were valid. Whether they were large enough to be of clinical (functional) importance, specifically in PLHIV, remains uncertain and is an area for future research. Follow-up studies to assess change over time would be useful for quantifying meaningful differences in PLHIV.

The kinematic patterns described above is similar to the age-related biomechanical plasticity of gait[232] often seen in older adults. This walking strategy involves a distal-to-proximal shift in muscle function and thus joint ROM[232] (in this study, elicited during dual task walking). The phenomenon of biomechanical plasticity is thought to most likely be related to changes in neural and musculoskeletal function.[478] The underlying mechanism in PLHIV may be similar, given the potential involvement of central neuromotor control hypothesised in the previous section. Specifically relating to muscle function, Scott et al.[121] found that PLHIV had difficulty in activating their knee extensor muscles (but not necessarily other muscles) and that this reduced central activation was associated with weakness and decreased specific force. Although these authors did not assess consequences for gait, perhaps a similar impaired activation could explain the reduced knee ROM, as well as the weaker knee extensors, noted in this cohort of PLHIV.

An interesting finding from the 3DGA was that when faced with the physical challenge of walking at a maximum speed, PLHIV had the capacity to increase their speed and overcome the impairments (kinematic as well as TSPs) noted for usual-paced or dual task gait. This may have implications for rehabilitation, as it seems that PLHIV may have the potential to improve their preferred gait pattern. However, whether the observed biomechanical impairments are reversible is not known and may need to be addressed in future research. It has been shown in older adults (including very fit individuals such as runners) that the age-related distal-to-proximal shift is resistant to exercise interventions, as such interventions failed to alter mechanical joint output.[232] However, exercise was still able to mitigate the effects of

neuromuscular impairment by improving leg strength[478] and is thus worth investigating in PLHIV – especially given the generally positive effects ascribed to aerobic as well as progressive resistive exercise in PLHIV.[479,480]

Maximal isometric lower limb muscle strength did not show many differences between PLHIV and SNP in this study (Table 8.2), with significantly lower strength (for PLHIV) only noted for knee extensors and flexors. Reduced knee extensor strength, in particular, has been cited as an independent risk factor for hip fracture and a predictor for mortality after fragility fracture in older adults.[481,482] This raises concern when considering the fall-related statistics and gait and balance impairments described in this study cohort. Although the minimum clinically important difference (MCID) for muscle strength changes in PLHIV is unknown, differences in thigh muscle strength of about 4% have been reported as clinically meaningful in patients with knee osteoarthiritis[483] in terms of resulting in better patient-reported outcomes. Whether these differences are large enough to impact on functional performance may be questioned; as increases of more than 20% still seemingly result in relatively small increases in gait speed.[232,484]

Considering the observed kinematic patterns described above, it is plausible that muscle activation and power, more so than strength, were responsible for the observed changes in PLHIV. This suggests that PLHIV may benefit more from exercise regimes that focus on improving the dynamic function of muscle, as opposed to isometric strength. The benefits of aerobic and progressive resistive exercise have already been reported in two Cochrane-method systematic reviews[479,480] but it may be worth investigating which exercises specifically result in meaningful improvements in gait function. Longitudinal research is warranted.

A cross-sectional study[44] conducted in Zimbabwe demonstrated that lower limb weakness, particularly of the proximal (hip) muscles, impacts on self-perceived function in PLHIV. In contrast to the current study, however, these authors found that knee flexor and extensor strength did not differ significantly between PLHIV and SNP, while ankle muscles (plantar- and dorsiflexors) and hip muscles (flexors, extensors, abductors and adductors) were significantly weaker in PLHIV.[44] The reason behind the discrepancy in observations is not clear, but may in part be attributed to the fact the PLHIV participating in the Zimbabwean study were on average significantly older than the current study group (70% of those participants being in an age range between 40 and 69 years), while the relatively smaller control group was mostly aged below 40 years (although the authors did adjust their analyses for demographic factors). Furthermore, although not significantly different from SNP, findings from the current study show a directional trend for hip muscles to be *stronger* in PLHIV compared to SNP, while

plantarflexors trended towards being weaker. This pattern would be in accordance with the age-related biomechanical plasticity of ageing gait as mentioned above. However, as comparing muscle strength differences between PLHIV and SNP was not a primary objective of this study, muscle strength results were not adjusted for age, gender or any other covariables; whilst Mhariwa et al.[44] performed regression analyses and adjusted for demographic factors. It was noted in Chapter 2 that evidence regarding muscle strength differences between PLHIV and SNP is contradictory. Further research regarding muscle strength as a primary outcome and using multivariable analyses is thus warranted to be able to draw more robust conclusions regarding strength differences, and whether such differences are of importance regarding gait function.

9.2.3. Composite score of gait variability

Variability defines the normal fluctuations that occur across multiple steps or strides [485] and increasing evidence supports the use of gait variability as a means of quantifying locomotion.[237,372,373,375] EGVI scores in this study revealed significantly lower variability in PLHIV relative to what is considered the norm in the reference population during usual and dual task gait. This finding was contrary to the expected increased gait variability in PLHIV, based on the U-shaped variation of gait variability, which implies that people who walk very slowly often have increased variability.[446] However, a real trend does seem to exist in these data, given that both gait speed and EGVI scores decreased in PLHIV under the dual task condition. Of importance, data from SNP in this study were used to construct a normative dataset for comparison – therefore, it can be said with confidence that the variability noted in PLHIV was significantly decreased relative to what would be considered normal *in this population* for usual-paced as well as dual task gait. These results remained after adjusted analyses (age and gender) and therefore appear valid.

The relationship between gait variability and fall risk has been suggested to be non-linear[486,487] – with those at either end of the spectrum (either having too much or too little variability) being at greater risk of falls. An “ideal” state of variability has been proposed for optimal functioning (in gait as well as in other biological systems), with the hypothesis that a large enough deviation from this state would be associated with pathology.[488] A decrease from the ideal state of variability renders the system too rigid and unchanging (e.g. a rigid gait pattern), while an increase makes the system unstable and chaotic.[488] Excessively decreased gait variability has been noted in various studies including those performed in older adults,[238,372,486,489,490] multiple sclerosis,[485] and Parkinson’s Disease.[372,491] The lower variability noted for PLHIV thus may indicate over-control of gait: a more rigid and less adaptable gait relative to SNP. Although

only an assumption, this may indicate that steps are carefully regulated in an attempt to increase stability.[238] This approach may be maladaptive and represent an inflexible system with fewer available degrees of freedom[485]; a state that has been associated with impaired capacity to adapt and adjust gait patterns[485] and which may thus potentially add to an increased fall risk in PLHIV when exposed to unexpected perturbations.

As established in Chapter 3, PLHIV are reported to have prolonged automated postural response latencies, with abnormal postural reflex regulation under unpredictable, but not predictable, perturbations.[62,262] Due to these response latencies, PLHIV may require more regularity of movement to avoid large or unexpected perturbations during walking.[485] It has been noted that gait speed should be considered when interpreting variability measures, as elders who walk slowly (speeds of less than 1 m/s) regardless of their fall status, have previously demonstrated lower variability than those who walk faster than 1 m/s.[487] The mean adjusted gait speed achieved for dual task walking by PLHIV in this study was 0.92 m/s (versus 1.11 m/s in SNP) and therefore may be associated with the low variability. Either way, since both slowed gait and decreased variability may pose fall risks, it remains evident that the gait of PLHIV is impaired in domains probably related to falls.

The choice of dual-task-related parameters also need consideration when interpreting findings from data collected under such conditions. It has been proposed that by combining the two rhythmic tasks of walking and backwards counting (which constitutes an attention as well as a rhythmic task), gait regularity may actually be emphasised.[492] This may explain why SNP also somewhat reduced their gait variability when performing a dual task. The effect was probably larger in PLHIV, as backwards counting has been proposed to have a particularly regulating effect in individuals with an inherently unstable gait and high fall risk[492] as may be the case for PLHIV participating in this study.

9.2.4. Static standing balance

This study revealed significant increases in mean centre of pressure (COP) excursion (ROM) in a mediolateral (ML) direction, as well as mean overall COP excursion in PLHIV under a dual task condition (Table 8.17). Increased COP excursion is a directional trend widely interpreted as indicative of poor postural balance control, as such a strategy may reflect the inability to recover from small postural perturbations.[493] The concerns regarding the interpretation of increased postural sway as “poor” balance were mentioned in Chapter 3. Nevertheless, increased COP excursions have been noted to relatively consistently predict falls in older adults (especially in a ML direction, when compensatory sideways-stepping fails).[494] The

findings of this study are also in agreement with the systematic review (Chapter 3), which found increased postural parameters in PLHIV, which were mostly elicited under challenging conditions (although these conditions were related to visual and sensorimotor input, while cognitive load was not investigated).

What these findings add, is that impaired postural control in PLHIV is evident in conditions where the visual and vestibular systems are left intact, leaving the somatosensory system and cognitive processing as potential mechanisms. The systematic review in Chapter 3 indicated that impaired postural balance in PLHIV was mostly elicited under conditions where visual input was reduced (eyes closed), while eyes open conditions did not reveal impairments in asymptomatic PLHIV.[62] Other studies have since been identified which report similar findings in asymptomatic PLHIV[323] with evidence to suggest that not only the visual but also the vestibular and proprioceptive systems are responsible for increased COP parameters in PLHIV.[322] However, none of these studies investigated dual task conditions. The findings from the current study suggest cognitive function as yet another contributor to impaired postural stability.

It was noted in Chapter 2 that PLHIV may use hyperactivation of adjacent brain areas to maintain a certain level of performance (the “brain reserve theory”), and that this strategy may fail under more challenging conditions.[101] Given the dual task condition employed in the current study, it may be deduced that deficits in cognitive processing largely contributed to the increased COP excursion noted in this cohort. Postural control has generally been considered an automated response to vestibular, somatosensory/proprioceptive and visual inputs, but evidence has since shown that postural regulation involves cognitive processes as well.[495–497] Dual task performance may reliably differentiate elderly fallers and non-fallers[498] and it has also been shown that postural sway increases when a dual task is applied in healthy younger adults (18 to 30 years old).[497] Although single leg stance (SLS) under dual task conditions has not previously been investigated in PLHIV, it seems likely to elicit differences given the cognitive domains commonly affected by HIV-1 infection.[298,323] Several neuropsychological theories on human information processing have been developed to attempt to explain the difficulties in the concurrent performance of dual tasks.[499] The capacity-sharing theory, for example, refers to a situation where a limited capacity in attention resources exists, so that the performance of two tasks that require attention causes a deterioration of at least one or both of the tasks.[497,499] This seems a feasible situation in this cohort of PLHIV, given that they tended to score lower on the cognition domain of the MOS-HIV (not a statistically significant, but a clinically significant difference), along with the observation that they made more mistakes in counting backwards whilst performing the SLS than they did in the seated practice session (although these

Cognitive Difficulty Scores [CDS] were not formally analysed or presented for the purposes of this dissertation).

Static standing tests measure but the simplest form of balance control, and considering the complexities of dynamic balance involved in gait, it is difficult to directly relate the current findings to gait impairments. What does seem clear, is that both gait and static balance deteriorated when PLHIV were subjected to a dual task, and both these motor tasks thus indicate impaired cognitive processing in PLHIV as a contributor to motor impairment. The subtle COP deviations may potentially indicate an early alteration in the postural balance system occurring before manifestation of gross balance impairment in clinical tests, as previously proposed in PLHIV.[323] However, PLHIV likely need more complex assessments of balance than single leg stance (also given the limited utility of clinical timed single leg stance tests noted for this cohort [Table 8.8]) to produce robust results. Tests involving dynamic balance or fatigued muscle states may be better suited.

Together, the findings from static posturography in this study suggest that subtle balance impairments occur in PLHIV under cognitively challenging conditions, which may precede gross manifestation of such impairments in simple clinical tests. The findings also align the widely proposed impaired cognitive processing related to divided attention in PLHIV. Given the prevalence of fallers in this sample of PLHIV, that impaired balance in PLHIV has been identified as a risk factor for falls[55] and that increases in COP excursion have commonly been associated with falls (albeit not yet proven in PLHIV), it may be that the increases in COP parameters in this sample had contributed to an increased fall risk. The implications are that balance training may be of value in PLHIV. However, more complex and dynamic balance testing or fatigued muscle states – both for use during posturography and as clinical tests – are needed to elicit meaningful results. Future laboratory studies could for example further investigate cortical and biomechanical factors that come into play during complex or unanticipated tasks in PLHIV by adding electroencephalography (EEG). Such studies may provide more insight into the motor planning capacity of PLHIV and its predictive value for adverse outcomes.

The impairments noted in this study are subtle (as noted with ageing adults) and manifested under challenging cognitive-motor conditions. The use of motion analysis technology enabled the identification of subtleties that would remain unnoticed during clinical observation alone. However, the use of technology demands a thorough understanding of its associated measurement errors and artefacts. Whilst the validity and reliability of the established gold standard in motion analysis (laboratory-based optical systems) have been proven; this study

demanded the collection of data at the respective clinical sites in a community setting. Therefore, the preliminary studies (Chapters 4 to 6) were aimed at assessing the rigour (validity and reliability) regarding the key outcomes (gait) using a newly acquired, portable motion analysis system. The next section discusses the key findings related to the validity and reliability of the biomechanical gait outcomes selected for analysis in this study.

9.3. Towards establishing robust three-dimensional gait analysis evidence in people living with HIV-1 infection: rigour of outcomes

9.3.1. Concurrent validity

At the start of this project, the myoMOTION inertial motion capture (IMC) system was newly acquired by the Stellenbosch University (SU) Movement Laboratory. The system needed to be assessed in terms of its validity and limitations regarding clinical gait assessment in a South African population and especially regarding custom-specified outcomes (as defined in Tables 4.5 and 4.6). It is particularly important for individual gait laboratories to establish reliability of its own operators and the technical limitations of the specific technology being used, along with the ability of the instrument to reliably measure the specific gait outcomes of interest for the clinical assessment at hand.[326]

The main finding from Study One (Chapter 5) was that the myoMOTION highly compares to the VICON-Plug-in-Gait (PiG) model output after accounting for biomechanical modelling offsets between systems. Confirming and expanding these findings in a rural South African population, Study Two (Chapter 6) confirmed that the validity of myoMOTION measurements was not compromised in participants from a rural setting, including PLHIV and SNP. However, because of an inherent and consistent offset between the systems/models (largely stemming from the myoMOTION model's calibration procedure, which differs from VICON-PiG as explained in Chapter 5), the myoMOTION and other systems such as VICON-PiG cannot be used interchangeably. However, these modelling offsets only affected average and discrete kinematic angles, and not TSPs and joint/segment ROM. Since only the myoMOTION was used for 3DGA in the cross-sectional field study, the kinematic offset errors for the discrete angles do not have serious implications for the study data in terms of comparing participants measured using the same system. However, it must be kept in mind that the field study data (particularly in terms of discrete outcomes) cannot readily be compared to data from studies where gait angles were measured by other systems. The implication is that follow up gait

analysis studies in PLHIV should carefully consider the measurement system and biomechanical model selected for 3DGA. The data from this study may prove useful for comparison to datasets obtained with the myoMOTION system, but cannot be compared to data from other systems when referring to absolute angles. Trends in ROM and TSPs, which are often better indicators of overall gait pattern, may however be comparable to other systems.

9.3.2. Absolute reliability

Schwartz et al.[313] proposed two potential sources of error which may affect variability in gait data: intrinsic and extrinsic. In this study, potential sources of variability may have included the reliability of the custom-defined gait outcomes (relating to methodology and measurement), the new myoMOTION system itself (instrumentation) and the individual (the PhD candidate in this case) setting up the calibration poses (rater).

All kinematic outcomes and TSPs showed clinically acceptable (kinematics) or acceptable/excellent (TSPs) within-session reliability. Because absolute reliability statistics such as the SEM provide results in the original unit of measurement, knowledge was also gained regarding the interpretation of gait outcomes in the cross-sectional field study. As expected, for kinematic angles, total ROM in a given movement plane was generally more reliable than discrete angles – this makes sense considering that the modelling differences dictate a different “starting” point and peak angles for each respective system, while there should be no reason for relative measures between these discrete angles to differ between systems designed to measure human motion.

The absolute reliability noted for the myoMOTION agrees with published reports for OMC-measured kinematic angles in the various movement planes in healthy adults.[318,327] In the cohort of PLHIV and SNP, the myoMOTION demonstrated good reliability for all angles except four, namely pelvis rotation at initial contact, peak knee flexion during stance, ankle plantarflexion at toe-off and peak ankle plantarflexion during the gait cycle. These findings may indicate that some key events of the gait cycle are inherently more variable, or that the myoMOTION and VICON systems were both more susceptible to (and potentially affected in different ways by) soft tissue movement at these events. For the field study, these outcomes were kept in the analysis to help establish a comprehensive picture of the gait pattern. However, the high measurement error likely significantly affected (in clinical terms) the group mean values observed for each of these listed outcomes. Therefore, these angles were flagged as outcomes that may not represent a true between-group difference, and were

considered not to be true descriptors of the gait deviations noted in PLHIV. Together, results indicated that accepting a MCID of 5° is generally reasonable for lower limb angles (except for hip rotation and the four discrete variables mentioned above) when using the myoMOTION for 3DGA.

9.3.3. The N-pose calibration as a source of error

The setup of the calibration N-pose for the myoMOTION was assessed as an important source of extrinsic error. This calibration needs to be performed multiple times within an analysis session with the system. It was determined that a trained rater can accurately and repeatably implement these N-poses. Although previous studies have assessed the repeatability of similar and different (i.e. functional) calibration poses,[309,500] repeatability has not been investigated for the myoMOTION, and not many have evaluated setup accuracy. Robert-Lachaine et al.[309] was one of the few which also assessed accuracy by defining a “perfect” pose-execution using 0°-criteria, as was done in this study. These authors demonstrated similar sagittal plane offsets (especially for the pelvis) to the present study. The observed values for pelvis offset agree with clinically reported anterior pelvic tilt values during normal stance in able-bodied adults,[501] confirming that the biomechanical constraints of normal human posture inherently affect the pose, but consistently (small standard deviations) and in an anatomically feasible manner.

This study further demonstrated clinically acceptable intra-rater repeatability for setting up all angles. Proper comparisons to the literature are hampered by heterogeneous published protocols and outcomes, but good intra-rater repeatability has generally been reported for setting up calibration poses, trending towards transverse angles being less so.[189,309] In this study, N-pose setup was determined to be the major contributor in offsets noted between myoMOTION and VICON. Throughout the field study, the researcher (PhD candidate) was the only operator responsible for setting up the N-pose, which decreased the risk of inconsistency in N-pose setup and its effect on subsequent gait measures. Overall, the good intra-rater repeatability noted for the N-pose setup, and the good within-session reliability of the myoMOTION support the use of this system across multiple participants or sessions. The gait impairments noted in PLHIV using this system, including parameters included in EGVI calculation, may be considered to be of scientific rigour.

9.4. Towards understanding potential implications: public burden and rehabilitation considerations

9.4.1. Burden implied by the participant profile

Despite to some extent reflecting the profile of South African PLHIV (for example in terms of age, gender and employment rates),[36] many factors hinder the generalisability of findings from this study to clinical settings in the larger South African context. On the other hand, some such factors may render the study findings more representative to the Cape Winelands or Western Cape, which is beneficial for drawing context-specific conclusions. Nevertheless, the profile of PLHIV who participated in this study does shed light on the complexity of chronic HIV and its potential consequences in a cohort where motor impairments persist, despite HAART.

9.4.1.1. Economic implications

This study revealed rigorously-measured locomotor impairments in a relatively young, economically-active group of PLHIV – of which almost half were unemployed. A young age group presenting with impairments represents a potential increase in economic burden on households and at community level. A recent study by Jakubowski et al.[502] indicated that PLHIV in Sub-Saharan Africa were more likely to have lost time from work due to illness and have incurred additional healthcare expenditures – these effects were linked to CD4+ count. The addition of movement impairments to systems already weakened by HIV disease factors may compound these effects.

The fact that more woman in South Africa are affected by HIV-1 infection[36] (being both physiologically and socially vulnerable to the effects of the disease) may also hold true in this study, as more than half of PLHIV were women (Table 8.1) (although this may also reflect the fact that women are more likely than men to attend clinics). Nevertheless, this phenomenon further shifts the burden of HIV-1 in terms of household dynamics, and children may also be affected. When women (being the main cares or even the head of household) suffer ill health and eventually become physically impaired, children may have to leave school prematurely to care for ill parents. At the same time, these households have to deal with the economic impact of a loss of income from the parent, or increased costs of healthcare utilisation (e.g. transport costs).[36]

Addressing morbidity by early targeting of the gait and balance impairments existing in PLHIV can ultimately yield substantial economic gains to the community and perhaps South Africa,

due to reduced healthcare utilisation and improved economic outcomes for vulnerable populations. Further studies need to confirm the potential of rehabilitation to reduce the economic impact and improve the well-being of all PLHIV in South Africa by including larger, more diverse samples, which may also allow for subgroup analyses.

9.4.1.2. Health resource implications:

The participant profile noted in this study illustrates the complex nature of chronic HIV. Participants suffered from many comorbidities such as depression/anxiety, chronic pain and potentially cognitive dysfunction. Many of these comorbidities have been associated with adverse outcomes such as functional decline – this escalates the effect that movement impairments may have on mobility function in PLHIV.

Young-to-middle-aged people suffering from movement impairments, comorbid to chronic conditions such as HIV-1 infection, may potentially decline even further in function as they live and age with these impairments. The implication is that long-term chronic health and rehabilitation care will be needed. Chronic care models have not yet been fully developed in South Africa.[63] This highlights the need to identify and effectively address movement impairments and confirms the need for research such as the current study.

9.4.2. Rehabilitation considerations

9.4.2.1. Health promotion

A healthy lifestyle should be promoted among PLHIV by physiotherapists and other health care workers, but this may go beyond the obvious. Adherence to HAART is vital for the treatment to effectively suppress viraemia, and should thus be improved. Research regarding HAART adherence has indicated that predictors and risk factors are region-dependent, behoving context-specific development of non-adherence profiles.[503,504] In resource-limited settings including South Africa, functional limitations, physical inactivity, chronic pain and reduced quality of life are amongst the factors associated with non-adherence to HAART,[7,505] emphasising the importance of addressing such risk factors in South African PLHIV and that physiotherapists may be very well suited to promote HAART adherence and prevent further secondary complications – given that these risk factors may at least in part be modifiable by rehabilitation.[506]

The sample in this (field) study had a relatively low CD4+ T-cell count (below 500 cells/μL, Table 8.5). Although almost all PLHIV were using HAART for at least six months or more, less than half had viral loads below the limits of detection. This observation may partly be due to

the fact that about a fifth of PLHIV in this sample reported non-adherence to HAART (Table 8.5) (which may even have been an underestimation, since these data are based on self-report). Together, increased chronic pain levels, lower cognitive function, more anxio-depression symptoms and more self-reported mobility problems may explain these non-adherence statistics. In the general population, it is known that chronic pain can lead to a vicious cycle in those affected, where avoidance of physical activity may lead to increased disability due to immobility and atrophy.[507] Interestingly though, it has been shown in South African PLHIV that chronic pain did not lead to the expected impairments in activity, and that PLHIV may suppress the effects of pain on activity due to a fear of stigma as well as financial stresses.[508] This would explain the observation that 44% of PLHIV in this study reported relatively high levels of physical activity despite also reporting chronic pain. However, almost 90% of PLHIV did not meet requirements for moderate physical activity (Table 8.3). A concerning finding by Hanass-Hancock et al.[40] was the observation of an association between HAART adherence and mobility. This finding suggested that people with mobility limitations may experience barriers when accessing healthcare or, alternatively, that poor adherence is associated with developing mobility problems. Physiotherapists need to be aware of the many risk factors for mobility disability which may co-exist in PLHIV and the importance of effective interventions aimed at promoting and improving physical activity and overall mobility in a complex population.

9.4.2.2. Prevention

In the general population, fall prevention (primary and secondary) is a critical health and prevention issue regarding the care of older adults.[494,509] The risk factors for falls are manifold, and many may be modifiable (e.g. impaired balance, muscle weakness and polypharmacy). Evidence suggests that fall risk increases with the number of risk factors; therefore, multifactorial interventions are advocated as effective strategies to reduce functional decline and prevent the associated burden of complications such as falls.[509]

Fall risk is usually not a concern in the average younger person – for example, a 36-year-old would not routinely be screened for fall risk. However, fall prevention may be of importance for younger individuals living with HIV. Not only are these people at a higher risk of falling (for example, a third of the young-to-middle-aged cohort of PLHIV in this study reported having at least one fall in the previous year, Table 8.6) but they may also be more likely to sustain a fracture when falling. This is due to the reduced bone mineral density commonly noted in PLHIV, as also demonstrated in this study (Tables 8.2 and 8.6). Fall prevention must become a priority among health care workers dealing with PLHIV.

Although the risk factors for falls amongst PLHIV are still being investigated, they do not necessarily seem unique to PLHIV or directly related to HIV disease markers (see Chapter 2, Section 2.5) – with common risk factors for falls in PLHIV including frailty, peripheral neuropathy, slowed gait, impaired balance, multimorbidity, and polypharmacy (Chapter 2, Section 2.5). The current sample demonstrated gait and balance impairments as already discussed, with a third of PLHIV also reporting nonantiretroviral polypharmacy and 8% reporting multimorbidity (Table 8.4). Falls pose a particular concern for PLHIV because of the prevalence of reduced BMD (almost 60% of PLHIV in this study suffered from either osteopaenia or osteoporosis).

It may be worth extrapolating from the high-quality evidence existing for the elderly that has recommended multifactorial risk assessments and screening to identify those at risk of falling, and specifically target risk factors existing in PLHIV as part of a tailored falls prevention programme (see also Section 9.4.2.3 below regarding the potential value of early screening in PLHIV). A systematic review[494] found strong evidence for the use of the Five-Times Sit-To-Stand (5STS) Test and gait speed assessments to predict falls among community-dwelling older adults. The review also supported the predictive value of laboratory-based assessments of postural sway and gait variability. Further investigating and incorporating such evaluation tools into comprehensive assessments of PLHIV may contribute towards improved falls prevention in this population and interventions in this younger population may need to specifically target intrinsic risk factors, such as mobility, strength/power, gait, and sensory impairment.

9.4.2.3. Early screening and rehabilitation

Early screening for motor impairments in PLHIV will make prevention and treatment rehabilitation more effective. Based on the findings from this study, the 5STS test is recommended for identifying physical impairment in PLHIV. This test is useful but not yet definitive. It is thus recommended as a test worth investigating further.

The recommendation of the 5STS test is based on the fact that this test (i) significantly correlated with quantitative, self-reported and fall-related outcomes in PLHIV and (ii) showed a high prevalence of impairment in PLHIV relative to SNP. It is especially important in a culturally-diverse country such as South Africa – with substantial inequalities and varying disease profiles between geographical regions[510] – that low-cost and pragmatic rehabilitation measures should be validated in context. Such evidence-based measures have the potential to contribute to cost-effective optimisation of rehabilitation outcomes.[60,510] It is important to note the limitations of the 5STS test at this early stage as a screening tool, and not a predictive measure or diagnostic tool. Screening

tests should be followed up by more targeted assessments and rehabilitation. As evident from the biomechanical findings and associated logical inferences discussed earlier in this chapter, interventions focusing on improving balance, lower limb muscle function and bone density may be most beneficial for PLHIV. However, we do not know at present whether the biomechanical impairments observed in PLHIV are reversible, and longitudinal follow up studies are needed to confirm this and make more conclusive recommendations.

In recognition of the dearth of high-level evidence regarding rehabilitation interventions for PLHIV, O'Brien et al.[170] recently compiled evidence-informed recommendations providing a guideline for rehabilitation with older adults living with HIV. More research is however required – and specifically for younger cohorts. The authors note that combining the areas of rehabilitation, HIV-infection and disability will enable further development of evidence-informed recommendations relevant to rehabilitation in the context of HIV-1 and contribute towards actionable recommendations to inform future practice.

9.4.2.4. Education

The International Classification of Function (ICF) is increasingly advocated as an overarching theme in the management of PLHIV.[37,511] Understanding HIV-associated impairments, functional limitations and participation restrictions is vital for effective rehabilitation.[23] While clinicians mostly manage the diagnosis and medical treatment of health conditions, functional ramifications and activity limitations have been reported to be a bigger priority to South African PLHIV in terms of participation and livelihood[40] and can only be mitigated through rehabilitation strategies. Physiotherapists need to be aware of movement and gait impairments with potentially serious functional consequences in PLHIV, and need to expand their skill sets to assess and manage such patients. Current South African statistics imply that every eighth patient seen by physiotherapists (or by physiotherapy students) in South Africa may also be a person living with HIV-1 infection.[36] In order to enable therapists to maximise functional outcomes in these patients, physiotherapeutic education programs (undergraduate as well as postgraduate) therefore need to shift the focus from a mostly biomedical approach (for example focusing on the pathology of HIV-1 infection) to a more rehabilitation-focused approach (for example the potential mobility problems associated with the condition, their consequences and potential treatment approaches – see also Figure 2.2 of how the ICF applies). The new knowledge regarding biomechanical impairments in PLHIV, as well as the risk of falls and the potential value of early screening, should be incorporated in undergraduate training, Continuous Professional Development (CPD) courses and other training workshops (potentially also including other healthcare workers).

CHAPTER 10
LIMITATIONS

The studies included in this dissertation have limitations that should be considered when interpreting the findings of the research. The limitations of the systematic review are included in Chapter 3 and thus not presented here.

10.1. Limitations of the validity and reliability studies (Chapters 4 to 6)

- Although VICON-Plug-in-Gait (PiG) served as the reference standard, the system is susceptible to faulty marker placement.[354,512] Nevertheless, marker placement was performed by the same laboratory-trained physiotherapist (the PhD candidate) throughout both laboratory-based studies, and participants with above-normal body mass index (BMI) were excluded from this project, which likely limited these effects.

- The measurement of gait biomechanics by the myoMOTION was only assessed under usual-paced conditions, which may specifically limit interpretation of the fast-paced data collected in the field study. Due to some participants demonstrating very slow gait speeds in the laboratory studies, observations regarding anticipated difficulties could be made regarding performance at such slow speeds. Difficulties were mostly related to missed event detection resulting in invalid or missed gait cycles, due to the fact that gait cycle detection by the myoMOTION involves the definition of peak angular velocity events. This observation affected data analysis for the field study to some extent as some trials with missed events were identified (n = 2). Unfortunately, the system's performance under fast-paced gait conditions remains uncertain and would most likely be affected by inertial measurement unit (IMU) movement. However, all field-study participants were of normal BMI and care was taken to securely fixate IMUs to the various body segments. Considerations regarding the tasks assessed in the laboratory-based studies were also made in the light of what was deemed pragmatic and reasonable regarding the time that the participants, who were transported from Worcester, had to spend in the motion analysis laboratory.

- Soft tissue artefact (STA) differences between systems were not specifically controlled (quantified). However, it may be argued that it is redundant to differentiate STA from

calibration errors for very small dynamic differences, as the combined STA- and calibration error was already below 5°.

- Between-day test-retest or inter-rater reliability was not investigated. However, reliability in terms of repeated IMU-placement is probably at least as good as the reliability of OMC marker-placement, since IMUs require no accurate placements or anatomical landmark identification. In addition, only one operator was involved throughout the project, and each participant was measured on one occasion only.

- A conservative approach was implemented to remove the average offset between waveforms estimated by the myoMOTION and VICON systems/models. Had a matrix approach been adopted, and segment rotations of the myoMOTION model been changed to adjust for modelling differences, more of the between-system error would have been compensated for. However, this is a complex and time-intensive method and was beyond the scope and pragmatic restraints of the current dissertation. The approach we adopted was considered sufficient for reliably illustrating the point that the differences in the system outputs are dominated by calibration offsets and not by IMU tracking, and that data provided by the system remains clinically usable. Removing the error even more strictly would in fact strengthen this point even more and is reserved for further analysis at a later stage.

- Both validity and reliability studies included predominantly female participants. However, these distributions also reflect the situation in the cross-sectional field study, and the influence of gender on gait kinematics are not well established (most evidence existing for some differences in coronal plane kinematics).[314,441]

- Estimates are limited by the small sample size, especially in the second study (Chapter 6). However, the magnitudes of measures of agreement, offset and reliability were similar within PLHIV and SNP groups, implying that the presence of HIV-1 did not affect the comparison between systems.

10.2. Limitations of the cross-sectional field study (Chapters 7 to 8)

- Findings of this study cannot be extrapolated to clinical settings in other provinces of South Africa. However, this limitation also reflects a strength as this sample is to a large extent representative of the HIV-seropositive population living in the Western Cape of South Africa

and thus provides context-specific evidence for use of the 5STS test in rural primary care clinics.

- It was decided not to apply Bonferroni corrections due to the strong correlations existing between individual gait variables,[457,513] and the fact that gait outcomes were pre-planned in this study. However, potential chance findings of statistical significance due to a Type I error cannot be excluded. To address the problem of a potential chance finding, relationships between gait outcomes that demonstrated to be statistically significantly different between groups were examined for clinical feasibility and described in the context of the other significant angles and TSPs. The rationale was that it would be unlikely for a chance finding of significance to be associated with significant differences in its contributing variables.

- Despite inflating the calculated sample size to 50 per group, missing trials for various tasks still led to a smaller number of outcomes being available for some analyses. For example, the dual task paradigm was only introduced later during the data collection protocol, after noting the importance of cognitive factors in PLHIV, along with the realisation that verbally-instructed fast walking may not be a reliable method.[451] Therefore, dual task data was only available for 41 PLHIV and 47 SNP. The impact of the late introduction of the dual task condition was even more apparent for static posturography data. In addition to the 12 participants for whom no such data were collected, one SNP had invalid dual task trials due to constant foot shuffling, two PLHIV had invalid trials due to shuffling and one PLHIV was unable to perform single leg standing under the dual task condition (unsafe). Dual task data were thus only available for 45 SNP and 40 PLHIV. Similarly, enhanced Gait Variability Index (EGVI) scores were calculated in only 42 PLHIV and 37 SNP for the usual-paced condition, and in 40 PLHIV and 33 SNP for the dual task condition. EGVI calculation requires a minimum of five absolute differences (at least 13 consecutive steps per trial),[372,375] which necessitated the exclusion of some participant datasets. This was mainly the consequence of the myoMOTION system failing to detect consecutive gait events under very slow gait speeds. It was additionally decided not to calculate the EGVI for fast-paced gait, due to problems with many participants not having enough valid *consecutive* (as opposed to total) strides per limb within a trial. Calculating the EGVI for this condition would thus not have yielded a valid outcome in terms of gait variability for comparison.

- Verbal instructions were provided to participants to walk as fast as they could (as if trying to catch a bus or taxi) in order to assess fast (maximum) walking speed. Compared to using

a metronome, for example, it was hoped that this method would facilitate more natural gait patterns at each speed. The reliability of this verbal instruction may be questioned in terms of truly eliciting the participants' maximum effort.[451]

- Centre of pressure (COP) data were only analysed for the dual task condition for the purposes of the current thesis – based on the results from the systematic review in Chapter 3 (that single leg stance differences only became apparent in more challenging conditions) and due to the fact that an eyes-closed single leg stance task may be too difficult and variable to reveal meaningful differences between groups.[514] Indeed, only 22 SNP and seven PLHIV were able to complete the full 30-second trial with eyes closed without shuffling, despite being allowed a practice attempt. Shorter time intervals from this condition will be analysed at a later stage, but for the purposes of this dissertation it was decided to present the zero- to 30-second time interval (full trial data) as this would provide the most meaningful data for COP outcomes[390] and would enable comparison to previous studies performed in PLHIV.[3,33,113] Thus, the dual task condition, maintained for 30 seconds, was deemed sufficient to elicit between-group differences in COP parameters and therefore to answer the research question.

- The reliability of the MatScan pressure mat was not tested specifically in the sample participating in this study. Unlike the myoMOTION, the MatScan is a widely used tool in research which has been proven to be valid and reliable for assessing the task at hand (single leg stance) and well as the basic COP parameters assessed in this study. Although not assessed specifically in PLHIV, these previous findings were noted in healthy adults as well as older adults. The movement of PLHIV was not expected to be vastly different from these populations and there was no reason to suspect that the device would be unreliable for measuring a simple task of static balance in PLHIV, using traditional/standard outcomes. Furthermore, the MatScan has proven useful in PLHIV before.[321–324] Nevertheless, this limitation should be kept in mind when interpreting the results from the static posturography since the measurement errors for COP velocity and excursion were not determined for intrinsic variability existing in this specific sample.

- Static balance was quantified simplistically, using basic traditional COP parameters, as has mostly been done in PLHIV. The ecological validity of these outcomes and the static posture is questionable, since single leg stance constitutes the simplest condition of postural control and the selected outcomes only address a small subset of the full balance repertoire. In addition, the fact that the single best effort trial out of three attempts was used

per participant may have led to some participants only achieving the successful trial in the third try, allowing a degree of habituation that does not occur when individuals suddenly lose their balance in daily life. Furthermore, the number of response strategies available to participants was restricted, i.e. by instructing participants to respond with foot-in-place (no shuffling or hopping allowed) and with arms crossed in front of the chest. The purpose of asking participants to cross their arms was to account for possible substitution efforts in maintaining balance with arm movements during testing.[467]

- Given the relatively low levels of formal education in this sample, a backwards counting task using units of three proved to be appropriate for most, but not all participants. Therefore a methodology as proposed by Swanenburg et al.[187] was adopted, to determine a suitable level of difficulty for each participant. However, it may have been that the task was still too difficult for some, resulting in performing the primary task (e.g. walking) whilst discarding the secondary task (i.e. counting) without any attempt to perform this second task accurately (e.g. careless and random counting). This was observed and addressed in a couple of participants; however, such cases may still have occurred without the researcher noticing and may have mitigated the effect of the dual task.

- Fall outcomes were based on retrospective self-report of events by participants, which may have resulted in an underreporting of falls, especially in those with cognitive impairment (e.g. forgetfulness). However, within the limitations of the study timeframe, prospective data collection was not possible.

- Despite initial attempts, it was not possible to match participant numbers on gender and age. The study was heavily dependent on the demographic of the participants that were also participating in the EndoAfrica study. Although it was initially envisioned to only use participants who were also enrolled in the EndoAfrica cohort, it became apparent that this methodology severely limited timely recruitment for the current study. In addition, many of the participants were already affected by a large appointment burden. The protocol was therefore amended to also include participants from the local community that were not participating in the EndoAfrica study, and the Paarl site was additionally added for data collection. However, these issues ultimately led to unequal age and gender distributions between PLHIV and SNP. These factors were controlled for statistically during data analysis of the biomechanical and clinical performance outcomes.

- Large numbers of steps are usually required for the accurate estimation of stride-to-stride variability.[237] This study used a limited number of steps, i.e. the absolute minimum required for calculating the EGVI. Larger numbers of steps are likely to provide more reliable results. Despite the portability offered by the myoMOTION system, available private space for gait analysis was still constrained at the clinical venues. The number of steps used in this study was the maximum that could be performed within these limited spaces.

CHAPTER 11
RECOMMENDATIONS

The research contained in this dissertation provides novel findings and presents a good foundation for future research. Based on the findings of the various studies, the following recommendations are made:

- To expand the use of the myoMOTION to populations with higher body mass indices (BMI), the effect that soft tissue artefacts (STA) may have on the measurement error of the myoMOTION needs to be established. Determining the psychometric properties of this system for higher BMIs would expand its usability among a wider population of people living with HIV-1 infection (PLHIV), who are also susceptible to obesity in the modern-day HAART era.

- The individual contribution of error sources to the validity of the myoMOTION should be further investigated by using a matrix approach to control for the biomechanical model differences. For example, raw signals from the myoMOTION can be used to align the local coordinate systems of the myoMOTION and VICON-PiG systems based on angular velocities during a 3D motion.[515]

- Due to the cross-sectional study design of the field study, no conclusions can be drawn regarding causality. Future high-quality prospective cohort studies are needed to establish whether HIV-1 leads to the development of biomechanical impairments at early ages, and whether the Five-Times-Sit-To-Stand (5STS) Test is a predictor of adverse outcomes including falls, which may either be addressed early in rehabilitation, or treated as preventative factors in at-risk PLHIV.

- Future studies should determine whether the biomechanical impairments noted in PLHIV are reversible following rehabilitation, which may be targeted at improving cognitive-motor function (e.g. cognitive training) and/or restoring a flexible gait pattern and a faster gait speed. However, care should be taken when implementing the latter approach before the underlying contributing factors to the kinematic deviations have been determined, including how these may relate to fall risk. The fact that PLHIV were able to tap into resources and walk with a pattern similar to SNP at a fast pace may imply that the noted gait impairments may be reversible. On the other hand, if fast walking and longer strides place PLHIV at a higher risk for falling due to exceeding their maximal threshold for safe walking, simply

altering these potentially compensatory parameters without addressing factors such as dynamic balance or inflexibility may actually increase their fall risk. Future studies should ascertain whether assuming a more normal pattern kinematic pattern and walking at a faster pace requires more effort from PLHIV, whether fast walking can be maintained with a normal kinematic pattern for extended periods of time, and whether fast walking with larger stride lengths increases fall risk in PLHIV.

- This study can only speculate about the neuromuscular patterns involved in the gait of PLHIV, such as impaired force and activation of lower limb muscles. An understanding of such patterns would be valuable and may guide the development of targeted rehabilitation strategies. Future studies should include comprehensive gait analysis protocols involving kinetics and electromyography (EMG) in PLHIV.

- The HIV-related reasons underlying the observed biomechanical impairments and poor chair rise performance can only be theorised in this cross-sectional study. Future appropriately-powered analyses of association involving sub groups according to HIV-specific and other clinical characteristics should be conducted to gain further insight. Such analyses would also reveal the ability of the 5STS to discriminate high-risk groups for poor performance within PLHIV, and the determination of relevant cut-off scores would yield the test more suited specifically to PLHIV, as opposed to basing interpretation on cut-offs determined in older adults.

- The value of the 5STS to screen for self-reported problems related to quality of life domains may warrant its use as a measure of treatment outcomes in PLHIV, in terms of functional performance and quality of life. Future research should ascertain the ability of the 5STS to serve as a measure of monitoring treatment outcomes over time in PLHIV.

- It would be of value to explore knowledge among South African physiotherapists and other first contact health care workers in primary care settings regarding the risk of specific gait and balance impairments in PLHIV, and the fact that fall risk may be increased. Data on referral patterns and utilisation of physiotherapy services, as well as the manner in which (if at all) the physiotherapeutic management of PLHIV are tailored towards high-risk patients would highlight areas that need to be addressed and incorporated in practice and policy.

- Relating to the previous point, awareness should be increased amongst South African physiotherapists and health professionals regarding the locomotor risks, including reduced bone mineral density and increased fall risks, which may occur in relatively young PLHIV. It may be of value to incorporate a quick, simple, no-cost tool such as the 5STS test as part of a standard assessment of PLHIV by first contact practitioners, with referral for rehabilitation and fall risk management (if the screening was not done by the physiotherapist themselves). Physiotherapists should also consider to screen PLHIV who consult them for other reasons (such as lower back pain) using the 5STS test. It must be emphasised that the test remains a screening tool to guide further intervention or testing, and should as such be followed up with appropriate methods such as manual muscle testing. Such assessment may suggest additional impairments that need further specific testing and treatment. This dual approach may restore or maintain normal function and prevent functional decline.

- This study suggests that the 5STS assessment may be a more valid test than the full PPB for screening for locomotor impairment in PLHIV, due to the high ceiling effects noted for the balance component of the full battery. This is a valuable finding, because it supports the use of the 5STS test when time and space is limited in clinical settings. However, use of the full PPB or the Six-Minute Walk Test in particular may still be of value in understanding PLHIV's experience of their mobility problem. It seems that these tests may also be more useful in older cohorts and should thus be assessed as such in future research. Clinically measured gait speed in particular may remain an important indicator of functional decline in PLHIV aged 50 years and older.[58]

- Regarding postural stability, future studies should implement complex and dynamic balance testing or fatigued muscle states to elicit meaningful results. Future laboratory studies could also investigate cortical and biomechanical factors that come into play during complex or unanticipated tasks in PLHIV by adding electroencephalography (EEG) to the protocol. Such studies may provide more insight into the motor planning capacity of PLHIV and its predictive value for adverse outcomes.

- The 5STS test as a stand-alone screening test revealed moderate correlations with 3D gait analysis and clinical outcomes. The search thus needs to continue for ways to render this test more sensitive to subtle gait and balance impairments in PLHIV. Adding a dual task to the testing protocol may be one option.

CHAPTER 12
CONCLUSION

HIV-1 is now a chronic condition. Not only is one in every eight South Africans living with the disease, but HIV-1 infection is also the number one cause of years lost to disability in the country. The virus itself, associated comorbidities and highly active antiretroviral therapy (HAART) (despite its success in prolonging life) are associated with impairments and declines in function that may develop into disability. South African rehabilitation professionals are faced with a larger, working-aged and evolving number of people living with HIV-1 infection (PLHIV) who are at risk of functional decline and need to consider the potential impact of HIV-1 on the rehabilitation system. Motor impairments have been noted in PLHIV since the virus was discovered, and remain a concern in the modern treatment era. Functional performance related to the lower limbs and walking ability is a particular concern in PLHIV. While the motor system is clearly affected by HIV-1, the literature regarding gait and balance impairments largely focuses on self-reported outcomes or clinical performance tests. Thus, a poor understanding of exactly why and how the motor system is affected, remained. This study found that PLHIV present with a slowed and less adaptable gait, and that biomechanical deviations exist in the presence of a dual task. These deviations resemble the biomechanical plasticity noted in elderly gait. In addition, PLHIV demonstrate postural stability deficits (increased centre of pressure excursion) whilst performing a dual task. The study further shows that the Five-Times Sit-To-Stand (5STS) Test is the most valid clinical test to screen for early gait deviations in a clinical setting. These findings were noted in a relatively young group of PLHIV, of which a third reported one or more falls during the past year. The findings not only improve understanding of the gait and balance of PLHIV, but also highlight the need to screen young-to-middle aged PLHIV for motor impairments by integrating standardised clinical tests. However, while the 5STS test is suggested as a potential screening tool for existing impairments, it remains unknown whether the test is predictive of falls, or whether the impairments screened for in PLHIV are reversible. In addition, whilst kinematics provide some insight into the basic gait pattern adopted, kinetic analyses will provide more information regarding the neuromuscular patterns. More research, especially clinical trials and follow-up studies, is needed to address these issues and to establish an empirical evidence base for recognising the importance of secondary prevention of motor impairments in PLHIV on a policy level. Identifying and addressing such impairments at an early stage can ultimately yield substantial economic gains due to reduced healthcare utilisation amongst PLHIV who will be living well into old age with this complex condition.

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APPENDIX A:
Ethics approval

UNIVERSITEIT•STELLENBOSCH•UNIVERSITY
jou kennisvennoot • your knowledge partner

Approval Notice
Response to Modifications- (New Application)

04-Mar-2016
Berner, Karina K

Ethics Reference #: N15/05/043
Title: Biomechanical analysis of specific motor impairments contributing to functional decline in adults with HIV/AIDS.

Dear Mrs Karina Berner,

The **Response to Modifications -** ***(New Application)*** received on **11-Dec-2015**, was reviewed by members of **Health Research Ethics Committee 2** via Expedited review procedures on **04-Mar-2016** and was approved.
Please note the following information about your approved research protocol:

Protocol Approval Period: **04-Mar-2016** -**03-Mar-2017**

Please remember to use your **protocol number** (**N15/05/043**) on any documents or correspondence with the HREC concerning your research protocol.

Please note that the HREC has the prerogative and authority to ask further questions, seek additional information, require further modifications, or monitor the conduct of your research and the consent process.

After Ethical Review:
Please note a template of the progress report is obtainable on www.sun.ac.za/rds and should be submitted to the Committee before the year has expired. The Committee will then consider the continuation of the project for a further year (if necessary). Annually a number of projects may be selected randomly for an external audit.
Translation of the consent document to the language applicable to the study participants should be submitted.

Federal Wide Assurance Number: 00001372
Institutional Review Board (IRB) Number: IRB0005239

The Health Research Ethics Committee complies with the SA National Health Act No.61 2003 as it pertains to health research and the United States Code of Federal Regulations Title 45 Part 46. This committee abides by the ethical norms and principles for research, established by the Declaration of Helsinki, the South African Medical Research Council Guidelines as well as the Guidelines for Ethical Research: Principles Structures and Processes 2004 (Department of Health).

Provincial and City of Cape Town Approval

Please note that for research at a primary or secondary healthcare facility permission must still be obtained from the relevant authorities (Western Cape Department of Health and/or City Health) to conduct the research as stated in the protocol. Contact persons are Ms Claudette Abrahams at Western Cape Department of Health (healthres@pgwc.gov.za Tel: +27 21 483 9907) and Dr Helene Visser at City Health (Helene.Visser@capetown.gov.za Tel: +27 21 400 3981). Research that will be conducted at any tertiary academic institution requires approval from the relevant hospital manager. Ethics

APPENDIX B:
Provincial Government of the Western Cape (Department of Health) permission: Worcester CDC

STRATEGY & HEALTH SUPPORT
Health.Research@westerncape.gov.za
tel: +27 21 483 6857; fax: +27 21 483 9895
5th Floor, Norton Rose House., 8 Riebeek Street, Cape Town, 8001
www.capegateway.gov.za

REFERENCE: WC_2016RP10_878
ENQUIRIES: Ms Charlene Roderick

Stellenbosch University
Private bag x1
Matieland
7602

For attention: Prof Faadiel Essop, Dr John Cockroft, Dr Linzette Morris, Prof Quinette Louw, Mrs Karina Berner

Re: Biomechanical analysis of specific movement impairments contributing to early functional decline in adults living with HIV/AIDS - Sub-study to the Cape Winelands HAART to HEART study

Thank you for submitting your proposal to undertake the above-mentioned study. We are pleased to inform you that the department has granted you approval for your research.

Please contact the following people to assist you with any further enquiries in accessing the following sites:

Worcester CDC	**Surina Neethling**	**023 348 8102**

Kindly ensure that the following are adhered to:

1. Arrangements can be made with managers, providing that normal activities at requested facilities are not interrupted.

2. Researchers, in accessing provincial health facilities, are expressing consent to provide the department with an electronic copy of the final feedback (**annexure 9**) within six months of completion of research. This can be submitted to the provincial Research Co-ordinator (Health.Research@westerncape.gov.za).

3. In the event where the research project goes beyond the *estimated completion* date which was submitted, researchers are expected to complete and submit a progress report (**Annexure 8**) to the provincial Research Co-ordinator (Health.Research@westerncape.gov.za).

4. The reference number above should be quoted in all future correspondence.

Yours sincerely

A T HAWKRIDGE.

DR A HAWKRIDGE

DIRECTOR: HEALTH IMPACT ASSESSMENT

DATE: 9/5/2016.

APPENDIX C:
Provincial Government of the Western Cape (Department of Health) permission: TC Newman (Paarl)

STRATEGY & HEALTH SUPPORT
Health.Research@westerncape.gov.za
tel: +27 21 483 6857; fax: +27 21 483 9895
5th Floor, Norton Rose House, 8 Riebeek Street, Cape Town, 8001
www.capegateway.gov.za

REFERENCE: WC_2016RP10_878
ENQUIRIES: Ms Charlene Roderick

Stellenbosch University

Private bag x1

Matieland

7602

For attention: Prof Faadiel Essop, Dr John Cockroft, Dr Linzette Morris, Prof Quinette Louw, Mrs Karina Berner

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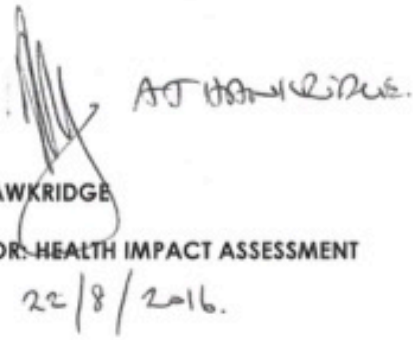
3. In the event where the research project goes beyond the *estimated completion* date which was submitted, researchers are expected to complete and submit a progress report (**Annexure 8**) to the provincial Research Co-ordinator (Health.Research@westerncape.gov.za).

4. The reference number above should be quoted in all future correspondence.

Yours sincerely



DR A HAWKRIDGE

DIRECTOR: HEALTH IMPACT ASSESSMENT

DATE: 22/8/2016.

APPENDIX D:
Informed consent form (first validity and reliability study: Student and staff volunteers)

TITLE OF THE RESEARCH PROJECT: The validity and reliability of the myoMOTION inertial motion capture system when measuring walking gait in HIV-seropositive as well as HIV-seronegative adults

REFERENCE NUMBER: N15/05/043
PRINCIPAL INVESTIGATOR: Karina Berner, Doctoral Candidate
ADDRESS: Division of Physiotherapy, Department of Interdisciplinary Health Sciences, Faculty of Medicine and Health Sciences, Stellenbosch University, Francie van Zijl Drive, Tygerberg, Cape Town, 8000
CONTACT NUMBER: 021 938 9667

You are being invited to take part in a research project. Please take some time to read the information presented here, which will explain the details of this project. Please ask the study staff any questions about any part of this project that you do not fully understand. It is very important that you are fully satisfied that you clearly understand what this research entails and how you could be involved. Also, your participation is **entirely voluntary** and you are free to decline to participate. If you say no, this will not affect you negatively in any way whatsoever. You are also free to withdraw from the study at any point, even if you do agree to take part.

This study has been approved by the **Health Research Ethics Committee at Stellenbosch University** and will be conducted according to the ethical guidelines and principles of the international Declaration of Helsinki, South African Guidelines for Good Clinical Practice and the Medical Research Council (MRC) Ethical Guidelines for Research.

What is this research study all about?

The aim of this study is to determine the precision and accuracy (reliability and validity) of a new three-dimensional motion analysis system (myoMOTION inertial motion capture system) recently acquired by the SU Central Analytical Facilities (CAF) 3D Human Biomechanics Unit. The performance of this system will be tested against the current reference standard, namely the VICON camera system, using about 24 HIV-negative and 8 HIV-positive adults. This study is the first phase of a bigger project, and the reason we are doing this study is to determine whether the myoMOTION system will be a suitable tool for use in the next study phase.
This study will be conducted in the CAF 3D Human Biomechanics Unit, Tygerberg Medical Campus. You will be responsible for your own transportation to and from the testing facility.

You will be asked to perform six to 10 normal walks along a measured walkway in the motion laboratory, while the two systems record you simultaneously. For this, you will need to change into shorts and a sleeveless sports top (females)/no shirt (males) and remove your shoes. A physiotherapist will measure your weight and height beforehand, as well as the range of motion of your joints. Before performing the walks, small reflective markers and motion sensors will be stuck to certain areas of your body using special double-sided tape. These will be removed

after testing. The expected duration of the entire testing session per participant (excluding transport to and from campus) will be about 90-120 minutes and will be scheduled at your convenience. Four participants will be tested per day, over a course of eight days (a total of 32 participants).

Why have you been invited to participate?

You have been invited to participate in this study because you responded to our advertisement and is an able-bodied adult that met the specific inclusion criteria.

What will your responsibilities be?

- You will be asked to go for confidential HIV-testing (available at Tygerberg Campus Health Services) at a time convenient for you (any time prior to the biomechanical analysis session), to confirm your status as HIV-negative.
- You will be expected to be available on the agreed-upon testing time (only one testing session is required per participant). You will also be responsible for your own transport to and from the testing facility.
- Woman will be asked to put on a sports top and shorts (that will be provided) and men will only wear shorts. We will then measure your weight and height, as well as the range of motion of your lower limb joints using a non-invasive measurement tool (goniometer).
- Small sensors will be put on your skin by means of a double-sided sticker. You will then be asked to walk up and down an area of 10 metres. In-between you will be asked to hold a static standing posture while the two systems calibrate. Only you and two researchers will be in the measurement area while you are walking. After the walking measurements have been completed, the sensors will be removed and you can put your own clothes back on.

HIV testing

As part of this research study, you will be asked to undergo an HIV test. Before agreeing to participate, it is important that you read and understand the following explanation of the HIV testing. *You may not participate in the study if you decide **not** to go for the HIV test.* However, the result of this test will not only determine whether you are suitable to continue with the research study, but could also have a profound influence on your health and lifestyle.

- **Purpose**

The purpose of the HIV test is to exclude any persons who are HIV-positive from this particular group of study participants, as HIV may influence the way that a person walks.

- **Procedure**

The HIV test will be done on a sample of blood drawn from your arm or obtained via a finger prick (rapid test). The test can detect antibodies that your immune system makes when HIV is present. The HIV antibody test is used to determine of you have been infected with HIV. An HIV test is extremely accurate if performed three months after exposure.

A negative test means that it is extremely unlikely that you are infected with HIV. If you had a recent expose (less than three months), an HIV test will need to be repeated to assure that you are not in the “window” period of HIV infection before the antibodies are present.

A confirmed positive test means that it is very likely that you have been infected with HIV. This test does not determine how advanced the illness is and is it not a test for AIDS. Medical care and additional testing will be needed to help plan treatment. *If you test is positive, you may not continue as a participant in the study*. You will be referred to an appropriate medical clinic for further testing and counseling.

If you test positive, you will not have any recourse to the researchers or study site for compensation or treatment.

- **Advantages and disadvantages of HIV testing**
  Advantages may include:
  - Making yourself available to healthcare and counseling for HIV which has many benefits
  - Preventing the transmission of HIV to your sexual partners
  - Informing your partner so he/she can also prevent the spread of HIV
  - Avoiding blood donations
  - Preventing mother to child HIV transmission

  Disadvantages may include:
  - Emotional stress, depression and despair
  - Stigmatisaion
  - Discrimination
  - Rejection by family, friends, sexual partners and/or spouse

These advantages and disadvantages should be carefully considered before signing the consent form.

Will you benefit from taking part in this research?

Although there are no personal benefits from taking part in this study, it will help us determine the validity and reliability of the new technology, so that it may be used in the next study phase. This next phase will involve using the new system in clinics to analyse the movement of adults living with HIV/AIDS, so that any impairments may be identified and a suitable screening test be selected for this population. Your participation in the current study will therefore benefit future patients.

Are there in risks involved in your taking part in this research?

Taking blood from your arm for the HIV test may cause bruising, infection, fainting, pain, or discomfort. All normal precautions will be taken to keep these side effects from happening.

If you do not agree to take part, what alternatives do you have?

Not applicable – no treatment is involved in this study.

Who will have access to your medical records?

Information gathered will be treated as confidential and shared only between the researchers involved. Any information of yours used in the thesis or subsequent publications will remain anonymous.

- **Confidentiality of HIV testing**

Your HIV test results will be matched to your name by a unique participant code assigned to your blood specimen – in this way, your identity will be protected. The test result will be kept confidential and only selected health-care providers will be informed on a need-to-know basis – this will include the principle investigator (KB) and any practitioners nominated by yourself.

Your HIV testing information and test results cannot be released to anyone without your written consent. A general consent for health care and information release does not cover HIV-related information. If you are found to be HIV-positive, you are not required to personally tell anyone about this diagnosis. However, it is very important to notify your sexual partners and those that might have been exposed to your blood.

What will happen in the unlikely event of some form injury occurring as a direct result of your taking part in this research study?

It is unlikely that any injury will occur as a result of taking part in this study.

Will you be paid to take part in this study and are there any costs involved?

You will receive compensation valued at R100 (e.g. grocery shopping voucher) for your time and effort to undergo HIV-testing. There will be no costs involved for you if you do take part in this study. In the event of a positive HIV test, you will be responsible the costs of any ongoing medical care and support.

Is there anything else that you should know or do?

- You can contact Ms Karina Berner at 021 938 9667 / **(email address)** if you have any further queries or encounter any problems.
- You can contact the **Health Research Ethics Committee** at 021 938 9207 if you have any concerns or complaints that have not been adequately addressed by your researcher.
- You will receive a copy of this information and consent form for your own records.
-

Declaration by participant

By signing below, I ……..…… agree to take part in a research study entitled **"The validity and reliability of the myoMOTION inertial motion capture system when measuring walking gait in HIV-seropositive as well as HIV-seronegative adults".**

I declare that:

- I have read or had read to me this information and consent form and it is written in a language with which I am fluent and comfortable.
- I have had a chance to ask questions and all my questions have been adequately answered.
- I agree to have blood drawn in order to undergo an HIV test as described before in order to determine my suitability for participation in this clinical study. I understand

that until my HIV status have been confirmed as being HIV-negative, my participation in the study is not guaranteed.

- I do not consider myself to be in a high-risk group for contracting HIV and have no reason to believe that I have been previously exposed.
- I understand I will be informed of the results of the test in confidence, and that I will be advised regarding further counseling and care, should the result be positive.
- I understand that should I be tested and found to be HIV-positive during the screening period, I cannot hold the study researchers liable for my treatment or care.
- I understand that taking part in this study is **voluntary** and I have not been pressurised to take part.
- I may choose to leave the study at any time and will not be penalised or prejudiced in any way.
- I may be asked to leave the study before it has finished, if the study doctor or researcher feels it is in my best interests, or if I do not follow the study plan, as agreed to.

Signed at (*place*) .....…..…….. on (*date*) ……...…….. .

....

Signature of participant **Signature of witness**

<u>Declaration by investigator</u>

I *(name)* ……..…… declare that:

- I explained the information in this document to ……..
- I encouraged him/her to ask questions and took adequate time to answer them.
- I am satisfied that he/she adequately understands all aspects of the research, as discussed above
- I did/did not use an interpreter. (*If an interpreter is used then the interpreter must sign the declaration below.*

Signed at (*place*) .....…..…….. on (*date*) ……...…….. .

Signature of investigator **Signature of witness**

APPENDIX E:
Informed consent form (second validity and reliability study: Community sample)

TITLE OF THE RESEARCH PROJECT: The validity and reliability of the myoMOTION inertial motion capture system when measuring walking gait in HIV-seropositive as well as HIV-seronegative adults

REFERENCE NUMBER: N15/05/043
PRINCIPAL INVESTIGATOR: Karina Berner, Doctoral Candidate
ADDRESS:
Division of Physiotherapy, Department of Health and Rehabilitation Sciences, Faculty of Medicine and Health Sciences, Stellenbosch University, Francie van Zijl Drive, Tygerberg, Cape Town, 8000
CONTACT NUMBER: 021 938 9667

You are being invited to take part in a research project. Please take some time to read the information presented here, which will explain the details of this project. Please ask the study staff any questions about any part of this project that you do not fully understand. It is very important that you are fully satisfied that you clearly understand what this research entails and how you could be involved. Also, your participation is **entirely voluntary** and you are free to decline to participate. If you say no, this will not affect you negatively in any way whatsoever. You are also free to withdraw from the study at any point, even if you do agree to take part.

This study has been approved by the **Health Research Ethics Committee at Stellenbosch University** and will be conducted according to the ethical guidelines and principles of the international Declaration of Helsinki, South African Guidelines for Good Clinical Practice and the Medical Research Council (MRC) Ethical Guidelines for Research.

What is this research study all about?

The aim of this study is to determine the precision and accuracy (reliability and validity) of a new three-dimensional motion analysis system (myoMOTION inertial motion capture system) recently acquired by the SU Central Analytical Facilities (CAF) 3D Human Biomechanics Unit. The performance of this system will be tested against the current reference standard, namely the VICON camera system, using 16 HIV-seropositive and 16 HIV-seronegative participants.

This study is the first part of a bigger project, which forms part of the HAART to HEART study being done in Worcester, and the reason we are doing this study is to determine whether the myoMOTION system will be a suitable tool for use in the next study phase. Although this smaller study is thus part of the HAART to HEART study, it has a different goal and is concerned with human movement. We are enrolling people from both Worcester and Paarl. Whether you choose to participate, or not, in this smaller study will not affect your current participation in the bigger study (if you are from Worcester), nor will it mean that you have to participate in any further research such as the bigger study (for example if you are from Paarl and not already involved in the bigger study).

This study will be conducted in the CAF 3D Human Biomechanics Unit, Tygerberg Medical Campus. Transport to and from the testing facility will be provided to you by the research team, as well as a light lunch on the day that you are tested, and you will be compensated for your time.

You will be asked to perform a number of normal walks along a measured walkway in the motion laboratory, while the two systems record you simultaneously. For this, you will need to change into shorts and a sleeveless sports top (females)/no shirt (males) and remove your shoes. A physiotherapist will measure your weight and height beforehand, as well as the range of motion of your joints. Before performing the walks, small reflective markers and motion sensors will be stuck to certain areas of your body using special double=sided tape. These will be removed after testing. The expected duration of the entire testing session per participant (excluding transport between Worcester/**Paarl** and Tygerberg) will be about one hour and will be scheduled at your convenience. Four participants will be tested per day, over a course of eight days (32 participants in total). Taking into account driving time and the fact that three other people will also be tested on the same day, the entire trip should take about six hours out of your day (once off).

Why have you been invited to participate?

You have been invited to participate in this study because you are an adult living in the Cape Winelands area that met the specific inclusion criteria and agreed to participate. If you are from Worcester, you have also been invited because you are already part of the bigger Cape Winelands HAART to HEART study.

What will your responsibilities be?

- You will be expected to be available for a trip to Tygerberg Medical Campus (transport and lunch provided, as well as compensation for your time) on the agreed-upon testing day and time (only one testing session is required per participant).

- Woman will be asked to put on a sports top and shorts (that will be provided) and men will only wear shorts. We will then measure your weight and height, as well as the range of motion of your lower limb joints using a non-invasive measurement tool (goniometer).

- Small sensors will be put on your skin by means of a double-sided sticker. You will then be asked to walk twelve times up and down an area of 10 metres, and stand still on a wooden block in between six of these walks. Only you and two researchers will be in the measurement area while you are walking. After the walking measurements have been completed, the sensors will be removed and you can put your own clothes back on.

Will you benefit from taking part in this research?

If a movement problem is identified, a physiotherapist will provide you with information on how to correct such a problem. Also, your participation will help us determine the validity and reliability of the new technology, so that it may be used in the next study phase. This next phase will involve using the new system in clinics to analyse the movement of adults living with HIV/AIDS, so that any impairments may be identified and a suitable screening test be selected for this population. Your participation in the current study will therefore also benefit future patients.

Are there in risks involved in your taking part in this research?

There are no risks involved in your taking part in this study.

If you do not agree to take part, what alternatives do you have?

You will not be denied any standard of treatment if you do not wish to take part in this research study. For example, if you feel that you have problems with movement, you are still welcome to consult the physiotherapist at your local clinic. Your participation in the main HAART to HEART study will also not be affected.

Who will have access to your medical records?

Only medical staff and the principal researcher will have access to your medical records. All information will be treated with respect and utmost confidentiality. Under no circumstances will your name or any form of identification be used. All information will also be treated as confidential and shared only between the researchers involved.

What will happen in the unlikely event of some form injury occurring as a direct result of your taking part in this research study?

It is unlikely that any injury will be suffered as a result of taking part in this study.

Will you be paid to take part in this study and are there any costs involved?

You will receive compensation (according to NHREC (2012) guidelines) for your time at a rate of R20 per hour, as well as R20 for the inconvenience of undergoing HIV testing and performing physical activities. This will be in the form of a food voucher. There will be no costs involved for you, if you do take part. Transport between Worcester CDC and Tygerberg Medical Campus will be provided, as well as a light lunch, free of charge.

Is there anything else that you should know or do?

- You can contact Mrs Karina Berner at **021 938 9300 /** (**email address)** if you have any further queries or encounter any problems.
- You can contact the Health Research Ethics Committee at 021 938 9207 if you have any concerns or complaints that have not been adequately addressed by your researcher.
- You will receive a copy of this information and consent form for your own records.

Declaration by participant

By signing below, I ……..……. agree to take part in a research study entitled **"The validity and reliability of the myoMOTION inertial motion capture system when measuring walking gait in HIV-seropositive as well as HIV-seronegative adults".**

I declare that:

- I have read or had read to me this information and consent form and it is written in a language with which I am fluent and comfortable.
- I have had a chance to ask questions and all my questions have been adequately answered.
- I understand that taking part in this study is **voluntary** and I have not been pressurised to take part.
- I may choose to leave the study at any time and will not be penalised or prejudiced in any way.
- I may be asked to leave the study before it has finished, if the study doctor or researcher feels it is in my best interests, or if I do not follow the study plan, as agreed to.
- I have consumed no alcohol today.

Signed at (*place*) .....…….. on (*date*) ……...…….. .

....

Signature of participant **Signature of witness**

Declaration by investigator

I *(name)* ……..…… declare that:

- I explained the information in this document to ……..
- I encouraged him/her to ask questions and took adequate time to answer them.
- I am satisfied that he/she adequately understands all aspects of the research, as discussed above
- I did/did not use an interpreter. (*If an interpreter is used then the interpreter must sign the declaration below.*

Signed at (*place*) .....…….. on (*date*) ……...…….. .

....

Signature of investigator **Signature of witness**

APPENDIX F:
Informed consent form (cross-sectional field study: Worcester)

TITLE OF THE RESEARCH PROJECT: Biomechanical analysis of specific movement impairments contributing to early functional decline in adults living with HIV/AIDS: Sub-study to the Cape Winelands HAART to HEART study

REFERENCE NUMBER: N15/05/043

PRINCIPAL INVESTIGATOR: Karina Berner, Doctoral Candidate
ADDRESS: Division of Physiotherapy, Department of Health and Rehabilitation Sciences, Faculty of Medicine and Health Sciences, Stellenbosch University, Francie van Zijl Drive, Tygerberg, Cape Town, 8000
CONTACT NUMBER: 021 938 9667

You are being invited to take part in a research project. Please take some time to read the information presented here, which will explain the details of this project. Please ask the study staff any questions about any part of this project that you do not fully understand. It is very important that you are fully satisfied that you clearly understand what this research entails and how you could be involved. Also, your participation is **entirely voluntary** and you are free to decline to participate. If you say no, this will not affect you negatively in any way whatsoever. You are also free to withdraw from the study at any point, even if you do agree to take part.

This study has been approved by the Health Research Ethics Committee at Stellenbosch University and will be conducted according to the ethical guidelines and principles of the international Declaration of Helsinki, South African Guidelines for Good Clinical Practice and the Medical Research Council (MRC) Ethical Guidelines for Research.

What is this research study all about?

- This study forms part of a bigger project, namely the Cape Winelands HAART to HEART study, which you are also a part of. The purpose of this smaller study is to look at the way you normally walk, as well as your balance, using a special portable movement analysis system, and to compare these findings with a short movement test, to see if they tell us similar things about your movement. If the movement test agrees with the movement analysis system, physiotherapists may use this test in clinics to identify movement problems in patients and start treating them at an early stage.
- We will also gather information about your own idea of your well-being, ability to do and remember things and whether you have ever fallen down in the last year, using short questionnaires, to see how this information compare to the way you move.
- This study will be done in a private room at a Stellenbosch University's Ukwanda campus, located next to Worcester CDC (transport will be provided to and from the clinic). We will need two test groups of about 40 participants each – a group of is HIV-seropositive and a group who is HIV-seronegative.

- You will be measured by a registered physiotherapist. Your body weight and height will be collected, as well as nerve testing of your feet, strength testing of your leg muscles and the amount of movement in your leg joints. The strength of your bones will also be measured. Measurements will not cause you any harm of discomfort.
- You will be asked to walk 3 times at a normal speed, 3 times at a fast speed and 3 times whilst counting aloud backwards, while the movement system records you. You will also be asked to stand on one leg on a mat that measures movement (for 30 seconds at a time) – 3 times with open eyes, 3 times with closed eyes and 3 times while you count backwards loudly. For this, you will need to change into shorts and a sleeveless sports top (women)/no shirt (men) and remove your shoes.
- Before performing the walks, small motion sensors will be stuck to certain areas of your body using special double-sided tape. These will be removed after testing. The expected duration of the entire testing session per person will be **between 1 ½ hours and 2 hours**. About 3 to 4 participants will be tested per day.
- We are selecting persons who are willing to participate in this sub-study from all persons who are also partaking in the main study. Everyone participating in the main study therefore has an equal chance of being selected for this study, and may participate should they match our study criteria.

Why have you been invited to participate?

You have been invited to participate in this study because you are part of the main HAART to HEART study and an adult living in the Cape Winelands that met the specific inclusion criteria.

What will your responsibilities be?

- You will be expected to be available on the agreed-upon testing time (only one testing session is required per person). We will transport 1 or 2 participants at a time to the nearby Ukwanda campus, where testing will be done. The entire time that you will be away, will be about 2 hours; we will also transport you back to Worcester CDC.
- You will be expected to fill in two short questionnaires, to find out about your medical conditions, pain, whether you have ever fallen down in the past year or are afraid of falling, how you feel about your memory and concentration, and how you feel about doing daily activities.
- Woman will be asked to put on a sports top and shorts (which will be provided) and men will only wear shorts. We will then measure your weight and height, as well as nerve symptoms in your feet. We will also measure the range of motion of your leg joints using a simple measurement tool. The strength of your muscles will also be tested with a hand-held device.
- The strength of your bones will be tested by placing your foot in a machine for a few seconds. This will not hurt or be uncomfortable. This test is not a diagnosis, but only a screening test. This means that it gives us an idea of how strong your bones are, and whether it might be necessary to investigate or manage this further. You will receive a copy of your results.
- We will make some activities more difficult by asking you to count backwards out loud while you walk or while you stand on one leg. We will let you practice beforehand. The purpose is not to see how well you count, but rather to see if you move differently while your attention is focused on an additional activity.

- You will perform a short physical test which evaluates walking and balance – the activities (5 times sit-to-stand, some balance tests and a short walk) will be timed with a stopwatch.
- Small sensors will be put on your skin by means of a "Velcro" strap or a double-sided sticker. You will then be asked to walk three times up and down an area of 10 metres as you normally walk, three times at a fast speed and three times while you count out loud. You will also be asked to stand on one leg on a special mat that measures movement, first with your eyes open, then with your eyes closed and then while you count. You will do these three times for 30 seconds. After the movement measurements have been completed, the sensors will be removed and you can put your own clothes back on.

Will you benefit from taking part in this research?

If a movement problem is identified, a physiotherapist will provide you with information on how to correct such a problem. Your participation in this study will also benefit future patients, as we will learn more about movement impairments in your population and which test would be best for physiotherapists to use for identifying such problems. Appropriate treatment can then be started earlier for future patients.

Are there in risks involved in your taking part in this research?

There are no risks involved in taking part in this study.

If you do not agree to take part, what alternatives do you have?

You will not be denied any standard of treatment if you do not wish to take part in this research study. For example, if you feel that you have problems with movement, you are still welcome to consult the physiotherapist at your local clinic.

Who will have access to your medical records?

Only medical staff and the principal researcher of the HAART to HEART study will have access to your medical records. All information will be treated with respect and utmost confidentiality. Under no circumstances will your name or any form of identification be used. The principle researcher of the smaller study will not have direct access to your medical file, but will receive relevant medical information from the principle researcher of the HAART to HEART study. For example, it is important for this study that we know you HIV-status and medical history (e.g. whether you suffer from Diabetes). This information will also be treated as confidential and anonymous, and shared only between the researchers involved.

What will happen in the unlikely event of some form injury occurring as a direct result of your taking part in this research study?

It is unlikely that any injury will occur as a result of taking part in this study.

Will you be paid to take part in this study and are there any costs involved?

You will receive compensation for your time at a rate of R10 per hour (according to NHREC (2012) guidelines) if you participate in this study**.** This will be in the form of a food voucher. There will be no costs involved for you, if you do take part.

Is there anything else that you should know or do?

- You can contact Mrs Karina Berner at **021 938 9300** / (**email address**) if you have any further queries or encounter any problems.
- You can contact the **Health Research Ethics Committee** at 021 938 9207 if you have any concerns or complaints that have not been adequately addressed by your researcher.
- You will receive a copy of this information and consent form for your own records.

Declaration by participant

By signing below, I ……..……. agree to take part in a research study entitled **"Biomechanical analysis of specific movement impairments contributing to early functional decline in adults living with HIV/AIDS: Sub-study to the Cape Winelands HAART to HEART study".**

I declare that:

- I have read or had read to me this information and consent form and it is written in a language with which I am fluent and comfortable.
- I have had a chance to ask questions and all my questions have been adequately answered.
- I understand that taking part in this study is **voluntary** and I have not been pressurised to take part.
- I may choose to leave the study at any time and will not be penalised or prejudiced in any way.
- I may be asked to leave the study before it has finished, if the study doctor or researcher feels it is in my best interests, or if I do not follow the study plan, as agreed to.

Signed at (place) .....…..…….. on (date) ……...……...

.....	.....
Signature of participant	**Signature of witness**

Declaration by investigator

I (name) ……..…… declare that:

- I explained the information in this document to ……..
- I encouraged him/her to ask questions and took adequate time to answer them.
- I am satisfied that he/she adequately understands all aspects of the research, as discussed above
- I did/did not use an interpreter. (If an interpreter is used then the interpreter must sign the declaration below.

Signed at (place) .....…..…….. on (date) ……...…….. ...

.....	.....
Signature of investigator	**Signature of witness**

APPENDIX G:
Informed consent form (cross-sectional field study: Paarl)

TITLE OF THE RESEARCH PROJECT: Biomechanical analysis of specific movement impairments contributing to early functional decline in adults living with HIV/AIDS: Sub-study to the Cape Winelands HAART to HEART study

REFERENCE NUMBER: N15/05/043
PRINCIPAL INVESTIGATOR: Karina Berner, Doctoral Candidate
ADDRESS: Division of Physiotherapy, Department of Health and Rehabilitation Sciences, Faculty of Medicine and Health Sciences, Stellenbosch University, Francie van Zijl Drive, Tygerberg, Cape Town, 8000
CONTACT NUMBER: 021 938 9300 / 021 938 9896

You are being invited to take part in a research project. Please take some time to read the information presented here, which will explain the details of this project. Please ask the study staff any questions about any part of this project that you do not fully understand. It is very important that you are fully satisfied that you clearly understand what this research entails and how you could be involved. Also, your participation is **entirely voluntary** and you are free to decline to participate. If you say no, this will not affect you negatively in any way whatsoever. You are also free to withdraw from the study at any point, even if you do agree to take part.

This study has been approved by the **Health Research Ethics Committee at Stellenbosch University** and will be conducted according to the ethical guidelines and principles of the international Declaration of Helsinki, South African Guidelines for Good Clinical Practice and the Medical Research Council (MRC) Ethical Guidelines for Research.

What is this research study all about?

- This study forms part of a bigger project, namely the Cape Winelands HAART to HEART study, which is currently being conducted in Worcester. The purpose of this smaller study is to look at the way you normally walk, as well as your balance, using a special portable movement analysis system. We will then compare these findings to those of a short movement test, to see if they tell us similar things about your movement. If the movement test agrees with the movement analysis system, physiotherapists may use this test in clinics to identify movement problems in patients and start treating them at an early stage.
- We will also gather information about your own idea of your well-being, ability to do and remember things and whether you have ever fallen down in the last year, using short questionnaires, to see how this information compare to the way you move.
- This study will be done in a private room in the TC Newman clinic in Paarl (we are also currently testing participants in Worcester). We will need two test groups of about 40 or more participants each – a group of is HIV-seropositive and a group who is HIV-seronegative.

- You will be measured by a registered physiotherapist. Your body weight and height will be collected, as well as nerve testing of your feet, strength testing of your leg muscles and the amount of movement in your leg joints. The strength of your bones will also be measured. Measurements will not cause you any harm of discomfort.
- You will be asked to walk 3 times at a normal speed, 3 times at a fast speed and 3 times whilst counting aloud backwards, while the movement system records you. You will also be asked to stand on one leg on a mat that measures movement (for 30 seconds at a time) – 3 times with open eyes, 3 times with closed eyes and 3 times while you count backwards out loud. For this, you will need to change into shorts and a sleeveless sports top (women)/no shirt (men) and remove your shoes.
- Before performing the walks, small motion sensors will be stuck to certain areas of your body using special double-sided tape. These will be removed after testing. The expected duration of the entire testing session per person will be between 90 minutes and 2 hours. About 3 to 4 participants will be tested per day.

Why have you been invited to participate?

You have been invited to participate in this study because you are an adult, attending the TC Newman clinic as an out-patient, you are living in the Cape Winelands district and meet the specific inclusion criteria.

What will your responsibilities be?

- You will be expected to be available on the agreed-upon testing time (only one testing session is required per person). Participation in the study will take about 2 hours of your time.
- You will be expected to fill in two short anonymous questionnaires, to find out about your medical conditions, pain, whether you have ever fallen down in the past year or are afraid of falling, how you feel about your memory and concentration, and how you feel about doing daily activities.
- You will also be asked questions about your medical history, exercise, lifestyle and habits – your answers will be kept anonymous.
- Woman will be asked to put on a sports top and shorts (which will be provided) and men will only wear shorts. We will then measure your weight and height, as well as nerve symptoms in your feet. We will also measure the range of motion of your leg joints using a simple measurement tool. The strength of your muscles will also be tested with a hand-held device.
- The strength of your bones will be tested by placing your foot in a machine for a few seconds. This will not hurt or be uncomfortable. This test is not a diagnosis, but only a screening test. This means that it gives us an idea of how strong your bones are, and whether it might be necessary to investigate or manage this further. You will receive a copy of your results.
- We will make some activities more difficult by asking you to count backwards out loud while you walk or while you stand on one leg. We will let you practice beforehand. The purpose is not to see how well you count, but rather to see if you move differently while your attention is focused on an additional activity.

- You will perform a short physical test which evaluates walking and balance – the activities (5 times sit-to-stand, some balance tests and a short walk) will be timed with a stopwatch.
- Small sensors will be put on your skin by means of a "Velcro" strap or a double-sided sticker. You will then be asked to walk three times up and down an area of 10 metres as you normally walk, and three times at a fast speed. You will also be asked to stand on one leg on a special mat that measures movement, first with your eyes open and then with your eyes closed. You will do this three times for 30 seconds. After the movement measurements have been completed, the sensors will be removed and you can put your own clothes back on.

Will you benefit from taking part in this research?

If a movement problem is identified, a physiotherapist will provide you with information on how to correct such a problem. Your participation in this study will also benefit future patients, as we will learn more about movement impairments in your population and which test would be best for physiotherapists to use for identifying such problems. Appropriate treatment can then be started earlier for future patients.

Are there in risks involved in your taking part in this research?

There are no risks involved in taking part in this study.

If you do not agree to take part, what alternatives do you have?

You will not be denied any standard of treatment if you do not wish to take part in this research study. For example, if you feel that you have problems with movement, you are still welcome to consult the physiotherapist at your local clinic.

Who will have access to your medical records?

Only the principal researcher of this study (Mrs. K Berner, a registered physiotherapist) will have access to your medical records. For example, it is important for this study that we know your HIV-status and medical history (e.g. whether you suffer from Diabetes). All information will be treated with respect and utmost confidentiality. Under no circumstances will your name or any form of identification be used or linked to your medical information, or any of the questions that you answer during the study.

What will happen in the unlikely event of some form injury occurring as a direct result of your taking part in this research study?

It is unlikely that any injury will occur as a result of taking part in this study.

Will you be paid to take part in this study and are there any costs involved?

You will receive compensation for your time at a rate of R20 per hour (according to NHREC (2012) guidelines) if you participate in this study, as well as an additional R10 for the inconvenience of performing the physical activities. This will be in the form of a food voucher. There will be no costs involved for you, if you do take part.

Is there anything else that you should know or do?

- You can contact Mrs Karina Berner at**: 021 938 9300 / 021 938 9896 / (email address)** if you have any further queries or encounter any problems.
- You can contact the **Health Research Ethics Committee** at 021 938 9207 if you have any concerns or complaints that have not been adequately addressed by your researcher.
- You will receive a copy of this information and consent form for your own records.

Declaration by participant

By signing below, I ……..…… agree to take part in a research study entitled **"Biomechanical analysis of specific movement impairments contributing to early functional decline in adults living with HIV/AIDS: Sub-study to the Cape Winelands HAART to HEART study".**

I declare that:

- I have read or had read to me this information and consent form and it is written in a language with which I am fluent and comfortable.
- I have had a chance to ask questions and all my questions have been adequately answered.
- I understand that taking part in this study is **voluntary** and I have not been pressurised to take part.
- I may choose to leave the study at any time and will not be penalised or prejudiced in any way.
- I may be asked to leave the study before it has finished, if the study doctor or researcher feels it is in my best interests, or if I do not follow the study plan, as agreed to.
- I have not consumed any alcohol today.

Signed at (place) .....…..…….. on (date) ……...……...

.....	.....
Signature of participant	**Signature of witness**

Declaration by investigator

I (name) ……..…… declare that:

- I explained the information in this document to ……..
- I encouraged him/her to ask questions and took adequate time to answer them.
- I am satisfied that he/she adequately understands all aspects of the research, as discussed above
- I did/did not use an interpreter. (If an interpreter is used then the interpreter must sign the declaration below.

Signed at (place) .....…..…….. on (date) ……...…….. ...

.....	.....
Signature of investigator	**Signature of witness**

APPENDIX H:
Health ABC Physical Performance Battery (PPB)

Participant code: _____ **Date: _____**

Health ABC Physical Performance Battery

1. Repeated Chair Stands

Instructions: Do you think it is safe for you to try and stand up from a chair five times without using your arms? Please stand up straight as quickly as you can five times, without stopping in between. After standing up each time, sit down and then stand up again. Keep your arms folded across your chest. Please watch while I demonstrate. I'll be timing you with a stopwatch. Are you ready? Begin

Grading: Begin stop watch when subject begins to stand up. Count aloud each time subject arises. Stop the stopwatch when subject has straightened up completely for the fifth time. Also stop if the subject uses arms, or after 1 minute, if subject has not completed rises, and if concerned about the subject's safety.. Record the number of seconds and the presence of imbalance. Then complete ordinal scoring.

Time: _____sec (if five stands are completed)

2. Balance Testing

Begin with a semi-tandem stand (heel of one foot placed by the big toe of the other foot). Individuals unable to hold this position should try the side-by-side position. Those able to stand in the semi-tandem position should be tested in the full tandem position. Once you have completed time measures, complete ordinal scoring.

a. Semi-tandem Stand

Instructions: Now I want you to try to stand with the side of the heel of one foot touching the big toe of the other foot for about 10 seconds. You may put either foot in front, whichever is more comfortable for you. Please watch while I demonstrate.

TIME HELD: ____ seconds

b. Tandem Stand

Instructions: Now I want you to try to stand with the heel of one foot in front of and touching the toes of the other foot for 10 sec. You may put either foot in front, whichever is more comfortable for you. Please watch while I demonstrate.

Grading: Stand next to the participant to help him or her into the side-by-side position. Allow participant to hold onto your arms to get balance. Begin timing when participant has feet together and lets go.

TIME HELD: ____ seconds

Participant code: _____ **Date: _____**

c. Single Leg Stance:

Instructions: Stand with your spine as vertical as possible, with your arms hanging down. Lift you're the leg of your choice and hold as long as possible.

Grading: Stand next to the participant and help him or her to assume the single leg stance position. Allow the participant to hold onto your arms to get balance. Begin timing when the participant lets go.

TIME HELD: _____ seconds

Total Balance: semi-tandem+ full tandem + single leg stance: _____/90 sec

3. 6 meter walk

Instructions: This is our walking course. If you use a cane or other walking aid when walking outside your home, please use it for this test. I want you to walk at your usual pace to the other end of this course. Walk all the way past the other end of the tape before you stop. I will walk with you. Are you ready?

Grading: Press the start button to start the stopwatch as the participant begins walking. Measure the time take to walk 6 meters. Then complete ordinal scoring.

Time: _____ sec (Calculation: 6 meters/_____ seconds = _____ m/sec)

4. Narrow Corridor Test (6 meters)

Instructions: Walk at your usual pace but stay between the lines of tape.

Grading: If participant steps outside the tape 2/more times this constitutes a failure. Up to 3 trials for two valid times are allowed. The average of the two trials is taken.

.

Trial 1: _____ seconds
Trial 2: _____ seconds
Trial 3: _____ seconds **Average time: _____ seconds**

Developed based on Simonsick EM et al. Measuring higher level physical function in well-functioning older adults: expanding familiar approaches in the Health ABC study. J Gerontol A Biol Sci Med Sci. 2001; 56: M644-9.

APPENDIX I:
Dual tasking sheet

FAMILIARISATION

Participant sits comfortably. Instruction: **"Count aloud backwards, in counts of (*7 / 3 / 2 / 1*), starting from *(select random number between 80 - 99*). Try to count as accurately as possible. You have 30 seconds."** *(Examiner times 30 seconds with stopwatch.)*
To calculate Cognitive Difficulty Score (CDS), circle the relevant options below – this practice-round is used to confirm the appropriate difficulty level per participant → select the difficulty level where the participant makes the least mistakes:

Cognitive difficulty score, taking into account task difficulty and mistakes made during tasking.[187]		
Difficulty counting backwards (units used)	**Mistakes made (Y/N)**	**Cognitive difficulty score**
1	YES	1
1	NO	2
2	YES	3
2	NO	4
3	YES	5
3	NO	6
7	YES	7
7	NO	8

CLINICAL TESTS (timed with stopwatch)

1) SIX-METRE WALK AT USUAL PACE, while counting down backwards in units of _____ (select 7 / 3 / 2 / 1), starting from _____(select random number between 80 and 99).

Time taken to complete walk (seconds):	
Number of mistakes:	
Calculated Cognitive Difficulty Score (refer to table):	

2) **SIX-METRE NARROW WALK** at usual pace, while counting down backwards in units of _____ (select 7 / 3 / 2 / 1), starting from _____(select random number between 80 and 99).

Time taken to complete walk (seconds):	
Number of mistakes:	
Calculated Cognitive Difficulty Score (refer to table):	

3) **SINGLE LEG STANCE WITH EYES OPEN**, while counting down backwards in units of _____ (select 7 / 3 / 2 / 1), starting from _____(select random number between 80 and 99).

Time stance held (seconds; max 30):	
Number of mistakes:	
Calculated Cognitive Difficulty Score (refer to table):	

3D ANALYSIS (3 TRIALS EACH – RANDOMISE ORDER)

1) **SINGLE LEG STANCE** on pressure mat with eyes open and arms crossed, while counting down backwards in units of _____ (select 7 / 3 / 2 / 1), starting from _____(select random number between 80 and 99).

	TRIAL 1	**TRIAL 2**	**TRIAL 3**
Time stance held (seconds):			
Number of mistakes:			
Cognitive difficulty score (refer to table):			

2) **WALKING AT USUAL PACE**, while counting down backwards in units of _____ (select 7 / 3 / 2 / 1), starting from _____(select random number between 80 and 99).

	TRIAL 1	**TRIAL 2**	**TRIAL 3**
Gait speed: *(*extract from software)*			
Number of mistakes:			
Cognitive difficulty score (refer to table):			

NOTES

- Order of balance tasks (single, dual, with and without vision) to be changed randomly to control for effects of fatigue and learning.
- **Cognitive task:**
    - Counting backwards using units of 7's.
    - Ask participant to count backwards as accurate as possible in 30 seconds as an initial practice-round. If units of 7 are too difficult – use units of 3's, 2s or 1's instead, as appropriate.
    - Starting-number selected at random from range between 80 – 99.[187]
    - Counting must be controlled throughout for accuracy and all mistakes should be noted.
    - No feedback on performance should be given during testing.
    - Evaluation of performance: Difficulty (7s, 3s, 2s or 1s) of subtraction-units, and number of mistakes made by participant [187] – dichotomized into "mistakes: yes" and "mistakes: no".
    - Use the above to define six performance scores.[187] The lowest score is designated a 1: when mistakes are made when counting backwards using 1's. The highest score (8) is given when counting down in 7's without mistakes (refer to the "Cognitive Difficulty Score" table for scoring).

APPENDIX J:
EuroQol Five-Dimensions Five-Levels questionnaire

Health Questionnaire

English version for South Africa

By placing a tick in one box in each group below, please indicate which statements best describe your own state of health TODAY.

Mobility

I have no problems in walking about ❑

I have some problems in walking about ❑

I am confined to bed ❑

Self-Care

I have no problems with self-care ❑

I have some problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

Usual Activities *(e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑

I have some problems with performing my usual activities ❑

I am unable to perform my usual activities ❑

Pain / Discomfort

I have no pain or discomfort ❑

I have moderate pain or discomfort ❑

I have extreme pain or discomfort ❑

Anxiety / Depression

I am not anxious or depressed ❑

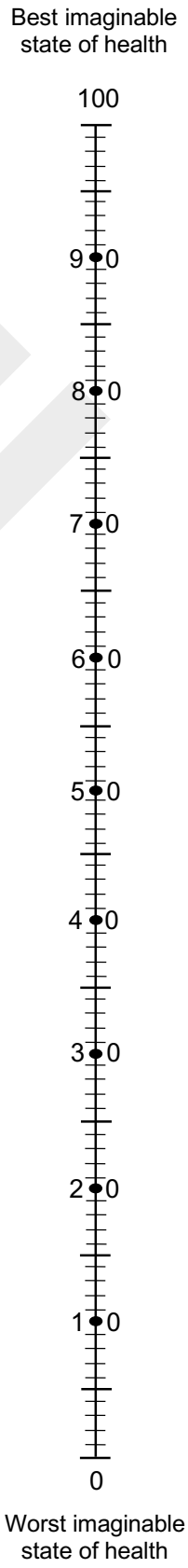
I am moderately anxious or depressed ❑

I am extremely anxious or depressed ❑

To help people say how good or bad their state of health is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale, in your opinion, how good or bad your own health is today. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your state of health is today.

Your own state of health today



APPENDIX K:
Field study data collection form

Project title: Biomechanical analysis of specific movement impairments contributing to early functional decline in adults living with HIV/AIDS: Sub-study to the Cape Winelands HAART to HEART study

Ethics approval nr: N15/05/043

CONFIDENTIAL

IDENTIFICATION CODE: HIVP2_		
Date and time:		
Assessment by:		
Research assistant:		
Age:		
Sex:		
HIV status	SNP	PLHIV

KOGNITIEWE FUNKSIE (vanuit die MOS-HIV vraelys)

(English on next page)

Merk asseblief ‘n blokkie by elke vraag:

		Die heeltyd	Meeste van die tyd	Baie van die tyd	Sommige van die tyd / somtyds	‘n Klein bietjie van die tyd	Nooit nie
Hoe gereeld, tydens die **laaste 4 weke:**							
a.	Was dit moeilik om te redeneer en probleme op te los, byvoorbeeld, om planne te maak, om besluite te maak, of om nuwe dinge te leer?	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐
b.	Het jy dinge vergeet wat onlangs gebeur het, byvoorbeeld, waar jy iets neergesit het of wanneer jy afsprake gehad het?	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐
c.	Was dit moeilik om jou aandag vir lank op enige aktiwiteit te hou?	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐
d.	Was dit moeilik om dinge te doen waar jy moes konsentreer en dink?	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐

COGNITIVE FUNCTIONING (from MOS-HIV questionnaire)

Please tick a box for each question:

			All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
10.	How much of the time, during the **past 4 weeks:**							
	a.	Did you have difficulty reasoning and solving problems, for example, making plans, making decisions, learning new things?	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐
	b.	Did you forget things that happened recently, for example, where you put things and when you had appointments?	1 ☐	2 ☐	3☐	4 ☐	5 ☐	6 ☐
	c.	Did you have trouble keeping your attention on any activity for long?	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6☐
	d.	Did you have difficulty doing activities involving concentration and thinking?	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐

PYN (vanuit die MOS-HIV vraelys)

(English on next page)

1. Hoeveel liggaamlike pyn het jy gedurende die **afgelope 4 weke** ervaar?
   (Merk 'n blokkie)

Geen	Net effens	Matig	Redelik	Ernstig	Baie ernstig
1☐	2☐	3☐	4☐	5☐	6☐

2. Gedurende die **afgelope 4 weke**, hoeveel het pyn ingemeng met jou normale werk (insluitend werk buite die huis en huiswerk)?
   (Merk 'n blokkie)

Glad nie	Effens	Redelik	Heelwat	Vreeslik baie
1☐	2☐	3☐	4☐	5☐

PAIN (from MOS-HIV questionnaire)

1. How much bodily pain have you generally had during **the past 4 weeks**?

   (Check one)

None	Very mild	Mild	Moderate	Severe	Very severe
1☐	2☐	3☐	4☐	5☐	6☐

2. During the **past 4 weeks**, how much did pain interfere with your normal work (or your normal activities, including work outside the home and housework)?

   (Check one)

Not at all	A little bit	Moderately	Quite a bit	Extremely
1☐	2☐	3☐	4☐	5☐

✍ Antwoord ook asseblief die volgende vrae so eerlik as moontlik, tot op die bladsy waar die navorser vir u gewys het om te stop**. Onthou, u is welkom om 'n vraag te vra as u iets nie verstaan nie!**

✍ *Please also answer the following questions as honestly as possible, up to where the researcher has shown you where to stop.* ***Remember, you are welcome to ask a question if you don't understand some of the questions!***

AFDELING A: DOMINANTE HAND & VORIGE FRAKTURE / *SECTION B: HAND DOMINANCE & PREVIOUS FRACTURES*		
1. Is u links- of regs-handig? / Are you left- or right handed?	LINKS / LEFT	REGS / RIGHT
2. Het u al ooit 'n been in u liggaam gebreek? / *Have you ever broken a bone in your body?*	JA /YES	NO /NEE
>> Indien **NEE** – beweeg asb aan na **Afdeling B** / *If **NO** – please move on to **Section B**.*		
3. Indien **JA** – watter been, en hoe lank terug was dit? / *If **YES** - which bone and how long ago did it happen?* _____ 3.1 Beskryf asseblief hoe dit gebeur het dat u die been gebreek het (baie kortliks) / *Please describe how this fracture happened (Very briefly):* _____ _____		
AFDELING B: BINNE-AARSE DWELM-GEBRUIK / *SECTION B: INTRA-VENOUS DRUG USE*		
Het u al ooit enige dwelm-middels vir uself ingespuit met 'n naald, wat nie deur 'n dokter voorgeskryf is nie? / *Have you ever taken any drugs using an injection, that was not prescribed by a docter?*	JA / YES	NEE / NO
AFDELING C: MIV-MEDIKASIE / *SECTION C: HIV-MEDICATION* **☞Indien u NIE 'n MIV-positiewe deelnemer is nie, beweeg asseblief aan na Afdeling D / *If you are NOT a HIV-positive participant, please move on to Section D.***		
Ons wil graag uitvind hoe gereeld u tans antiretrovirale medisyne gebruik, en of u dalk ooit vergeet om dit te neem / *We would like to know how often you are taking your antiretroviral medication, and if you maybe sometimes forget to take it.* **Maak asseblief 'n sirkel om die opsie hieronder wat u huidige gebruik van MIV-medikasie die beste beskryf** / *Please circle the option below that best describes your current use of HIV-medication:* *(*blaai asb om */ please turn to the next page)*		

0	My dokter het nie MIV-medikasie vir my voorgeskryf nie (bv gebruik slegs vitamiene) / *My docter has not prescribed me any HIV-medication (antiretroviral medication) (for example, only using vitamins)*
1	MIV-medikasie is vir my voorgeskryf, maar ek verkies om dit nie te neem nie / *HIV-medication was was prescribed to me, but I prefer not to use it.*
2	Ek het begin om my MIV-medikasie te neem, maar het intussen heeltemal gestop / *I have started to use my HIV-medication, but I have now stopped completely.*
3	Ek het begin om MIV-medikasie te gebruik, maar gebruik tans minder as wat voorgeskryf is / *I have started to use HIV-medication, but I am currently taking less than the prescribed amount.*
4	Ek het begin om MIV-medikasie te gebruik, maar vergeet baie kere om my pille te neem (vergeet meer as 2 keer in 'n week) */ I have started using HIV-medication, but I often forget to take my dosage (forget more than 2 times per week).*
5	Ek het begin om MIV-medikasie te gebruik en neem dit presies soos die dokter voorgeskryf het (ek mis NOOIT meer as 1 tot 2 dosisse in 'n week nie) / *I have started using HIV-medication and I take it exactly as the doctor prescribed it (I NEVER miss more than1 to 2 dosages per week).*

AFDELING D: OEFENING / *SECTION D: EXERCISE*

Wanneer u die volgende paar vrae beantwoord, dink asb aan 'n gewone of tipiese week / *While answering the next few questions, please consider a usual/typical week...*

1. Op 'n tipiese dag, neem u deel aan ENIGE tipe oefening of fisiese aktiwiteit (bv stap, fisiese werk, fietsry, draf ensovoorts) / *On a typical day, do you participate in ANY type of exercise or physical activity (such as walking, physical work, cycling, running etc.)?*	JA / YES	NEE / NO

1.1 Indien JA, wat is die aktiwiteit? */ If YES, what is the type of activity?* _____ ___

1.2 Hoeveel dae van die week doen u dit? / *How many days of the week do you do this?*

_____

1.3 Hoe lank oefen of beweeg u min of meer op 'n slag (bv "ek stap vir 30 minute")? / *How long, on average, do you exercise or move for? (for example "I walk for 30 minutes"):*

_____

AFDELING E: NEERVAL / *SECTION E: FALLING*

1. Het u ooit neergeval tydens die laaste jaar (daarmee bedoel ek, het u ooit op die grond/vloer neergeval, terwyl u gestap het)? / *Have you had any falls during the last year (by that I mean, did you fall to the ground, or to a lower level, while walking)?*	JA / *YES*	NEE / *NO*	ONSEKER / *UNSURE*

1.1. Indien JA op vraag 1, omtrent <u>hoeveel keer</u> het u neergeval in die <u>laaste jaar</u>? */ If YES to question 1, about how many times did you fall in the last year?*			
1.2 Indien JA op vraag 1 – beskryf asseblief kortliks waarom u geval het / wat gebeur het / *If YES to question 1 – please explain why you fell/what happened:*			
2. Het u ooit <u>neergeval</u> tydens die <u>laaste 3 maande</u>? */ Have you had any <u>falls</u> in the <u>last three months</u>?*	JA / *YES*	NEE / *NO*	ONSEKER / *UNSURE*
2.1 Indien JA op vraag 2, omtrent <u>hoeveel keer</u> het u neergeval in die <u>laaste 3 maande</u>? */ If YES to question 2, <u>how many times</u> did you fall in the <u>last three months?</u>*			
2.2 Indien JA op vraag 2 – beskryf asseblief kortliks waarom u geval het / wat gebeur het / *If YES to question 2 – please explain why you fell/what happened:*			
3. Is u ooit BANG DAT U GAAN VAL terwyl u loop of staan? / Are you ever AFRAID THAT YOU MAY FALL DOWN when walking or standing?	JA / *YES*	NEE / *NO*	ONSEKER / *UNSURE*
3.1 Indien u <u>soms bang is om te val,</u> verduidelik asseblief WAAROM u só sê: */ If you are sometimes afraid of falling, please explain WHY you say this:*			

✍ **U kan hier stop. BAIE DANKIE vir u earlike antwoorde op die vrae – dit is baie belangrik vir die sukses van hierdie navorsing!** */ You may stop here. THANK YOU VERY MUCH for your honest answers to the questions – this is crucial for the success of the research!*

MEASUREMENTS	
Body weight (kg)	
Height (cm)	
Leg length (ASIS to med malleolus)	
Foot length (mid heel to tip of longest toe)	

PERIPHERAL SENSORY NEUROPATHY ASSESSMENT OF LOWER LIMBS	
NORMAL	**AFFECTED (EXCLUDE)**
DOMINANCE (PREFERRED LEG FOR KICKING)	
LEFT	**RIGHT**

GONIOMETRY *(only note gross limitations, otherwise tick twice to indicate full and functional)*

Movement	Position	Notes	ROM (degrees)	
HIPS			**Left**	**Right**
Extension	Prone	Stabilise pelvis /ASIS to remain on plinth / knee in E (N = 10°~30°)		
Flexion	Supine	(N = 120°~135°)		
KNEES			**Left**	**Right**
Flexion	Supine	Hip & knee are flexed as heel moves toward buttock (N=135°)		
Extension	Prone; distal leg on bolster	(N= 0° / hyperE up to 10°-15°)		
ANKLES			**Left**	**Right**
Dorsiflexion	Prone with knee F	(N = 10° with kneeE / 20° with knee F)		
Plantarflexion	Prone with knee E	(N = 30°-50°)		

MUSCLE STRENGTH (HAND-HELD DYNAMOMETER)

MUSCLE	TRIAL #	**PEAK (N)**		NOTES
1. Hip flexors	1	L	R	Seated, hands resting in lap. Hips and knees flexed at 90°. HHD placed on ant aspect of thigh, proximal to knee joint.
	2	L	R	
	3 (if needed)	L	R	
2. Knee extensors	1	L	R	Seated, hands resting in lap. Hips and knees flexed at 90°. HHD placed on ant aspect of shank, prox to ankle joint. PT to stabilize self against wall.
	2	L	R	
	3 (if needed)	L		
3. Knee flexors	1	L	R	Seated, hands resting in lap. Hips and knees flexed at 90°. HHD placed on post aspect of shank, prox to ankle joint.
	2	L	R	
	3 (if needed)	L	R	
4. Hip abductors	1	L	R	Supine, hips and knees extended. HHD placed on lat aspect of shank, prox to ankle joint.
	2	L	R	
	3 (if needed)	L	R	
5. Ankle plantarflexors	1	L	R	Supine, ankle in plantargrade and hips and knees extended. HHD placed over metatarsal heads on sole of the foot. PT to stabilize self against wall.
	2	L	R	
	3 (if needed)	L	R	
6. Ankle dorsiflexors	1	L	R	Supine, with ankle relaxed and hips and knees extended. HHD placed over metatarsal heads on dorsum of foot.

	2	L	R	
	3 (if needed)	L	R	
7. Hip extensors	1	L	R	Prone, hips and knees extended. HHD placed on post aspect of thigh, prox to knee joint
	2	L	R	
	3 (if needed)	L	R	

BONE STATUS (QUANTITATIVE ULTRASOUND)

NON-DOMINANT FOOT = _____

	Result 1			**Result 2**			**Result 3**		
BQI									
T-score									
Z-score									
	N	**Osteopenia**	**Osteoporosis**	**N**	**Osteopenia**	**Osteoporosis**	**N**	**Osteopenia**	**Osteoporosis**

APPENDIX L:
Selected questions from EndoAfrica questionnaire

General Data

Date subject signed consent _____
((dd-mm-yyyy))

Date and time start of interview _____

Date of birth _____

Age when signed consent _____

Gender ◯ Male ◯ Female

Ethnicity
◯ Black
◯ White
◯ Coloured
◯ Indian
◯ Other (please specify)
◯ Refused

Ethnicity other _____

Education

What level of education have you completed?
☐ None
☐ Primary school
☐ High school
☐ ABET (Adult Basic Education Training)
☐ College/University/Other tertiary institution
(Tick all that apply)

Employment

Which of the following applies to your current employment situation?
◯ Unemployed
◯ Employed (full time)
◯ Employed (part time)
◯ Self-employed

Income

Do you or someone in your household receive a Government Social Grant? ◯ Yes ◯ No

What is the total of your household income per month?
◯ less than R1,000
◯ R1,000 - R4,999
◯ R5,000 - R9,999
◯ R10,000 - R20,000
◯ more than R20,000

Medical Background

MEDICAL BACKGROUND

Past

Have you had a heart attack in the past?	◯ Yes ◯ No
Have you been diagnosed with cancer in the past?	◯ Yes ◯ No
Have you previously had TB?	◯ Yes ◯ No
If yes, when did you previously have TB?	_____ (If patient cannot recall date, enter year (yyyy))
Have you had a stroke in the past?	◯ Yes ◯ No

Present

Do you have high blood pressure (hypertension)?	◯ Yes ◯ No ◯ Unknown
If yes, what year were you first diagnosed?	_____
Do you have a heart disease?	◯ Yes ◯ No ◯ Unknown
If yes, what year were you diagnosed?	_____
Do you have high cholesterol?	◯ Yes ◯ No ◯ Unknown
If yes, what year were you diagnosed?	_____
Do you have any other long lasting health problems? (For example: kidney stones, arthritis, asthma, bilharzia, malaria)	◯ Yes ◯ No
If yes, please specify what the health problem is and what year you were diagnosed?	_____
Do you currently have pulmonary Tuberculosis (TB)?	◯ Yes ◯ No
If yes, are you on treatment?	◯ Yes ◯ No
When did you start treatment?	_____ (If the patient cannot recall date, enter year (yyyy))

Diabetes

Do you have Diabetes ◯ Yes ◯ No

What type of Diabetes do you have?

◯ Type I Diabetes (also known as Juvenile Onset or Insulin Dependent Diabetes)
◯ Type II Diabetes (also known as Non-insulin Dependent Diabetes)
◯ Don't know

HIV

Are you HIV positive? ◯ Yes ◯ No

If positive, are you on ART? ◯ Yes ◯ No

Which line of ART are you on? ◯ 1st ◯ 2nd

What is the name of the ART? _____

For how long have you been on ART? _____
((weeks))

Date you were diagnosed with HIV? _____

If date unknown, how long ago approximately were you diagnosed with HIV

◯ In last year
◯ 2 - 5 years ago
◯ >5 years ago
◯ >15 years ago

Medications

Do you take any medications? ◯ Yes ◯ No

Which medications do you take?

☐ Beta blockers
☐ Statins
☐ Aspirin
☐ Calcium channel blockers
☐ ACE inhibitors
☐ Other
☐ Anti-inflammatory

If other, specify

_____

Lifestyle

Cigarette Smoking

Are you a smoker	◯ Yes currently ◯ In the past ◯ Never smoked
What type of cigarette do/did you smoke?	◯ Snuf ◯ Tobacco ◯ Dagga
On average, how many cigarettes do you smoke on the days that you smoke?	◯ More than 20 daily ◯ Less than 20 daily
If you have stopped, how long has it been since you last smoked (months)?	_____

Alcohol

Have you consumed an alcoholic drink within the past 12 months?	◯ Yes ◯ No
How often do you typically drink ?	◯ Daily ◯ 8 or more days a month ◯ Less than 8 days a month
At what age did you start drinking regularly (at least once a week)?	_____ ((answer in years))

What do you drink?

	Yes	No
Beer	◯	◯
Spirits (brandy, vodka, cane etc.)	◯	◯
Red Wine	◯	◯
White Wine	◯	◯
Other	◯	◯

When you drink beer, how many standard units do you typically have on a single occassion? (see reference card).	_____
When you drink spirits, how many standard units do you typically have on a single occassion? (see reference card).	_____
When you drink red wine, how many standard units do you typically have on a single occassion? (see reference card).	_____
When you drink white wine, how many standard units do you typically have on a single occassion? (see reference card).	_____

When you drink other, how many standard units do you typically have on a single occassion? (see reference card) and describe.

_____

Standard unit reference card

1 standard drink=

1 standard bottle or can of regular beer (340ml)

1 single measure of spirits (30ml)

1 medium size glass of wine (120ml)

How many drinks to you have on a weekend?

◯ Less than 5 ◯ 5 - 10
◯ More than 10
(Friday night to Sunday night)

Biochemical data / information from medical folder

FOLDER NUMBER: _____

HIV STATUS

HIV result	◯ Positive ◯ Negative ◯ Unknown
CD4 Count	_____ ((from file))
Viral Load	_____
Date of HIV diagnosis:	_____
ART:	_____
Other medication:	_____
Other blood results:	_____

Other relevant notes:

_____

_____

_____

_____

_____

_____

APPENDIX M:
Instructions for instrumented balance and gait analysis (field study)

1. Single leg stance (SLST)

The participant will be instructed as follows (eyes open): “Stand with both feet comfortably apart on the pressure mat. When I say “LIFT”, stand on any one leg by lifting the other foot so that the foot is ankle-height off the ground. Place your arms across your chest with your hands touching your shoulders and do not let your legs touch each other or the ground. Look straight ahead with your eyes open and focus on the cross on the wall *(*image of a cross will be fixated on a wall about 3 metres in front of the participant).* Hold this position as still and for as long as possible, or until I say stop”.

Instructions for the eyes closed condition will be: “Stand with both feet comfortably apart on the pressure mat. When I say “LIFT”, stand on any one leg by lifting the other foot so that the foot is ankle-height off the ground. Place your arms across your chest with your hands touching your shoulders and do not let your legs touch each other or the ground. Close your eyes once you have gotten in position. Hold this position as still and for as long as possible, or until I say stop”.

The participant will be instructed as follows for the dual task condition: “Stand with both feet comfortably apart on the pressure mat. When I say “START COUNTING”, start counting backwards aloud in units of *(7/3/2/1 – as previously determined)*, starting from *(random number chosen between 80 and 99).* Then, when I say “LIFT”, keep counting and stand on any one leg by lifting the other foot so that the foot is ankle-height off the ground. Place your arms across your chest with your hands touching your shoulders and do not let your legs touch each other or the ground. Look straight ahead with your eyes open and focus on the cross on the wall. Hold this position as still and for as long as possible, or until I say stop. It is important that you focus on counting as accurately as possible while you hold this position”.

Participants will be allowed a practice trial for all conditions, where after three test trials of 30 seconds each will be conducted. To prevent injury, a research assistant will stand close to the participant throughout the session. Leg dominance does not seem to affect one-legged balancing ability and participants will thus be allowed to choose a preferred stance leg [392].

2. Walking gait trials

The participant will perform a total of nine gait trials (ten metres) at (i) a self-selected speed (= 3x trials), (ii) fast speed (= 3x trials) and (iii) whilst performing a simultaneous cognitive task (= 3x trials). A 10-metre walkway will be marked on the floor with masking tape, with points indicated one metre before and after the measured length. Three practice walks will be done before the nine recording trials (at normal speed). Participants are to start walking on the command “GO”, one metre ahead of the measured walkway, and to stop and wait on the command “STOP” (one metre past the end of the walkway). Participants will be asked to turn around and repeat the procedure at the same speed three times, at fast speeds three times, and three times at preferred speed whilst counting aloud.

Instructions will be (normal speed): “Stand on the point marked with the masking tape. When I say GO, start walking in a straight line towards the other marker, at a normal, comfortable speed. Walk as normal as possible, as you would in everyday life. Only stop walking once I say STOP, turn around, and wait for the next instruction”.

For fast walking, the instruction will be: “Stand on the point marked with the masking tape. When I say GO, start walking in a straight line towards the other marker, as fast as you can without running; as if trying to catch a bus in time. Only stop walking once I say STOP, turn around, and wait for the next instruction”.

The dual tasking instruction will be: “Stand on the point marked with the masking tape. When I say “START COUNTING”, please start counting backwards aloud in units of *(7/3/2/1 – as previously determined)*, starting from *(random number chosen between 80 and 99).* Then, when I say GO, keep counting and start walking in a straight line towards the other marker, at a normal, comfortable speed. Focus on counting as accurately as possible whilst walking, but do not stop walking. Only stop walking and counting once I say STOP, turn around, and wait for the next instruction”.

APPENDIX N:
Publication PDF: Systematic review article

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BMC Musculoskeletal Disorders

RESEARCH ARTICLE Open Access

Objective impairments of gait and balance in adults living with HIV-1 infection: a systematic review and meta-analysis of observational studies

Karina Berner[1*], Linzette Morris[1], Jochen Baumeister[2] and Quinette Louw[1]

Abstract

Background: Gait and balance deficits are reported in adults with HIV infection and are associated with reduced quality of life. Current research suggests an increased fall-incidence in this population, with fall rates among middle-aged adults with HIV approximating that in seronegative elderly populations. Gait and postural balance rely on a complex interaction of the motor system, sensory control, and cognitive function. However, due to disease progression and complications related to ongoing inflammation, these systems may be compromised in people with HIV. Consequently, locomotor impairments may result that can contribute to higher-than-expected fall rates. The aim of this review was to synthesize the evidence regarding objective gait and balance impairments in adults with HIV, and to emphasize those which could contribute to increased fall risk.

Methods: This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. An electronic search of published observational studies was conducted in March 2016. Methodological quality was assessed using the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies. Narrative synthesis of gait and balance outcomes was performed, and meta-analyses where possible.

Results: Seventeen studies were included, with fair to low methodological quality. All studies used clinical tests for gait-assessment. Gait outcomes assessed were speed, initiation-time and cadence. No studies assessed kinetics or kinematics. Balance was assessed using both instrumented and clinical tests. Outcomes were mainly related to center of pressure, postural reflex latencies, and timed clinical tests. There is some agreement that adults with HIV walk slower and have increased center of pressure excursions and -long loop postural reflex latencies, particularly under challenging conditions.

Conclusions: Gait and balance impairments exist in people with HIV, resembling fall-associated parameters in the elderly. Impairments are more pronounced during challenging conditions, might be associated with disease severity, are not influenced by antiretroviral therapy, and might not be associated with peripheral neuropathy. Results should be interpreted cautiously due to overall poor methodological quality and heterogeneity. Locomotor impairments in adults with HIV are currently insufficiently quantified. Future research involving more methodological uniformity is warranted to better understand such impairments and to inform clinical decision-making, including fall-prevention strategies, in this population.

Keywords: HIV-1 infection, Gait, Postural balance, Falls

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Background

In Southern Africa, about 18.9% of adults aged 15–49 years are HIV-1-seropositive [1]. Both globally and in Sub-Saharan Africa, life-expectancy in people living with HIV (PLHIV) is now comparable to that of seronegative adults [2–4]. HIV/AIDS has evolved into a chronic condition due to the success of highly-active antiretroviral therapy (HAART) [2], but this is paralleled by increasing morbidity. In 1990, HIV/AIDS was the 33rd most important cause of disability-adjusted life years (DALYs) globally, but has since increased to fifth position [5]. In Sub-Saharan Africa, a high prevalence of HIV-associated disability, including impairments in mobility and motor function, is reported in PLHIV [6].

Gait and balance deficits have been reported in PLHIV despite controlled viral load [7–10] and are associated with reduced quality of life (QOL) [11, 12]. Current HAART regimes have less neurotoxic effects than older versions, and thus there is a lower risk of developing peripheral neuropathy [13]. However, the prevalence of peripheral neuropathy remains quite high among PLHIV (between 30% and 62%), and the prevalence of locomotor impairments remains a concern [14–17]. PLHIV have an increased incidence of falls [18–20], and fall rates among middle-aged PLHIV are comparable to that of seronegative older adults, aged 65 years and older [18]. These falls are attributed to balance impairments [20].

HIV-1 infection may compromise motor function at multiple levels of the nervous system [13]. Structural MRI-studies have shown that PLHIV present with white matter alterations, including reduced pontocerebellar tract integrity, leading to gait and postural instability [21]. It remains unclear whether gait and balance impairments noted in PLHIV are due to the disease process or its treatment [22]. One hypothesis is that these deficits occur as a complication of ongoing inflammation [14, 23, 24]. PLHIV, although adherent to treatment, experience non-AIDS defining complications resembling geriatric processes at an earlier than expected age [23, 25]. Chronic immune activation may be an underlying mechanism [23]. This accelerated aging manifests in middle-aged PLHIV as the accumulation of various co-morbidities, including frailty [23, 26].

Of further concern is that PLHIV are four times more at risk of fractures due to accelerated bone demineralization [27] and sarcopenia [28], and the proposed interplay between these conditions [29]. Low bone mineral density and sarcopenia are associated with balance problems and falls [28, 30]. These complications may be intrinsic to HIV infection (e.g. due to metabolic changes) or HAART-induced [31]. It has been suggested that the loss in bone mineral density is a result of increased bone turnover, especially during the first 12 to 24 months after HAART-initiation [32–34]. Various protease inhibitor (PI) or nucleoside reverse transcriptase inhibitor (NRTI) type antiretroviral therapies (ART) show a correlation with mitochondrial toxicity [22], damaging the structure and function of muscles. In addition, reduced central activation of muscles has also been reported in PLHIV, likely due to impaired oxygen utilisation [35].

Information is building that PLHIV demonstrate gait and balance impairments. However, owing to the variety of observational data, it is difficult to quantify the extent of impairment and to gain insight into which parameters are truly affected and clinically relevant. In elderly populations, several gait and balance parameters have been identified as independent predictors of fall risk, including spatiotemporal, kinetic, kinematic and clinical [36–39]. To the authors' knowledge, no previous systematic review has yet investigated objective impairments of gait and balance in PLHIV. The aim of this review is therefore to synthesize the evidence of objective impairments of gait and balance associated with HIV-1 infection, and to emphasize those which could contribute to increased fall risk. We also aimed to describe the evidence in relation to disease severity, treatment effects, task difficulty, and peripheral neuropathy.

Methods

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [40].

Criteria for considering studies for this review

Cohort, case-control and cross-sectional studies published in English as peer-reviewed journal articles were considered. Studies were included if they aimed to assess instrumented or non-instrumented objective parameters of gait and/or balance in adults (18–65 years of age) with HIV-1 infection, irrespective of gender. Given the expectation that there would be a paucity of information, studies with and without comparison groups were considered. Quantitative gait outcomes included, but were not limited to, kinematics, kinetics, spatiotemporal measures or clinical tests. Quantitative balance outcomes included, but were not limited to, biomechanical parameters such as center of pressure (COP) measures, and temporal measures via clinical tests. Studies were excluded if participants' age exceeded 65 years, as the prevalence of locomotor impairments is known to increase in older age even in healthy populations [41]. Studies aiming to assess HIV-Associated Neurocognitive Disorder using a neuropsychological test battery were also excluded, regardless of the use of a gross motor component, in an attempt to focus on studies with the primary aim of objectively assessing and describing gait or balance in PLHIV.

Search methods for identification of studies

Information sources

Six computerized bibliographic databases were searched, namely PubMed, Science Direct, EBSCOhost (CINAHL,

MEDLINE, Africa-Wide Information), Scopus, ProQuest Medical Library and Google Scholar. Following a preliminary search of PubMed, a comprehensive search strategy, including all relevant key word/terms and medical subject headings (MeSH) was developed and adapted for use in subsequent searching of the remaining databases. Search terms included: *(HIV-1 OR HIV Infection*) AND (motor function OR biomechanical phenomena OR gait OR postural balance OR locomotor function).* The search was restricted to papers published from inception of the database to March 2016. Reference lists of all identified documents were hand-searched to identify additional relevant evidence. In the event of missing data, an attempt was made to contact the authors.

Study selection

Titles and abstracts of all initial hits were screened by one reviewer (KB). When necessary, consultation with a second reviewer (QL) was pursued. All potential full texts were subsequently screened by these two reviewers, and eligibility criteria were applied independently. Any discrepancies regarding eligibility were discussed between reviewers to reach consensus.

Data collection and analysis

Methodological quality appraisal

One reviewer (KB) appraised the methodological quality of each included study using the National Institutes of Health (NIH) Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies [42]. The tool is designed to aid appraisal of internal validity (potential risk of selection-, information-, or measurement bias, or confounding) of cross-sectional and cohort studies and was therefore appropriate for this review. It comprizes 14 criteria. All criteria can be answered as "yes", "no", "cannot determine", "not applicable" or "not reported". All responses other than "yes" indicate risk of bias. Inherent to the design, cross-sectional studies automatically score "not applicable" on criteria 6, 7, 10 and 13. After all 17 articles were scored by the first reviewer, two of these were randomly selected for audit and independently scored by a second reviewer (LM). The scores assigned by each reviewer were compared by specifically discussing those criteria with discrepant scores. Consistent discrepancies were noted specifically for criteria 6, 10 and 13 for both studies – which were resolved after agreeing that these criteria should be scored as "not applicable" as per the instrument's instructions. Resultant total scores were similar; thus it was not deemed necessary for the second reviewer to score the remaining 15 articles as well. Each criterion was weighted equally in the overall grading, and studies were not excluded based on quality score, due to the expected dearth of information.

Data extraction

Data extracted from each study were summarized using a customized Excel spreadsheet, based on Cochrane forms. Information about sample demographics as well as the study aims, study design, known confounders to gait and balance, descriptors of HIV-disease, gait or balance analysis tool or test used, specific objective gait or balance outcomes, dose-response evidence, treatment effects, association of disease severity, association of peripheral neuropathy, findings and limitations of each study were extracted. Principle summary measures were means and standard deviations (SD).

Data analysis or synthesis

Narrative description of data was done using text summaries or tables as appropriate. For outcomes that were reported in at least two studies, a meta-analysis was conducted in Revman version 5.2, provided that homogeneity in the outcomes and samples existed regarding units of measurement, test conditions, gender and disease severity. Mean differences and 95% confidence intervals (CI) were calculated via a random effects model, provided that means and SD were reported, and were presented graphically as forest plots. Symptomatic (presenting with various symptoms of chronic HIV disease) and asymptomatic (asymptomatic HIV infection/clinically latent phase of HIV) subgroups of PLHIV were analyzed.

Results

Study selection

The initial search in March 2016 produced 799 total hits (Fig. 1). After removing duplicates and applying eligibility criteria, 93 potential titles remained. Thirty studies were subsequently excluded upon reading the abstracts. The main reasons for exclusion were that the outcome measures were not relevant to the review question, participants were not within the specified age range, and study design was inappropriate. Following full text review, the number of studies for inclusion was reduced to 17. Primary reasons for exclusion were inability to obtain full text, ineligible participants, no raw data and outcomes that were not relevant to the review question.

Study characteristics

Critical appraisal of study quality

Table 1 presents the methodological quality appraisal scores of the included studies, which ranged from fair to poor. A mean score of 40.34% was obtained, ranging from 7.14% (lowest internal validity amongst the included studies) to 57.14% (strongest internal validity amongst the included studies).

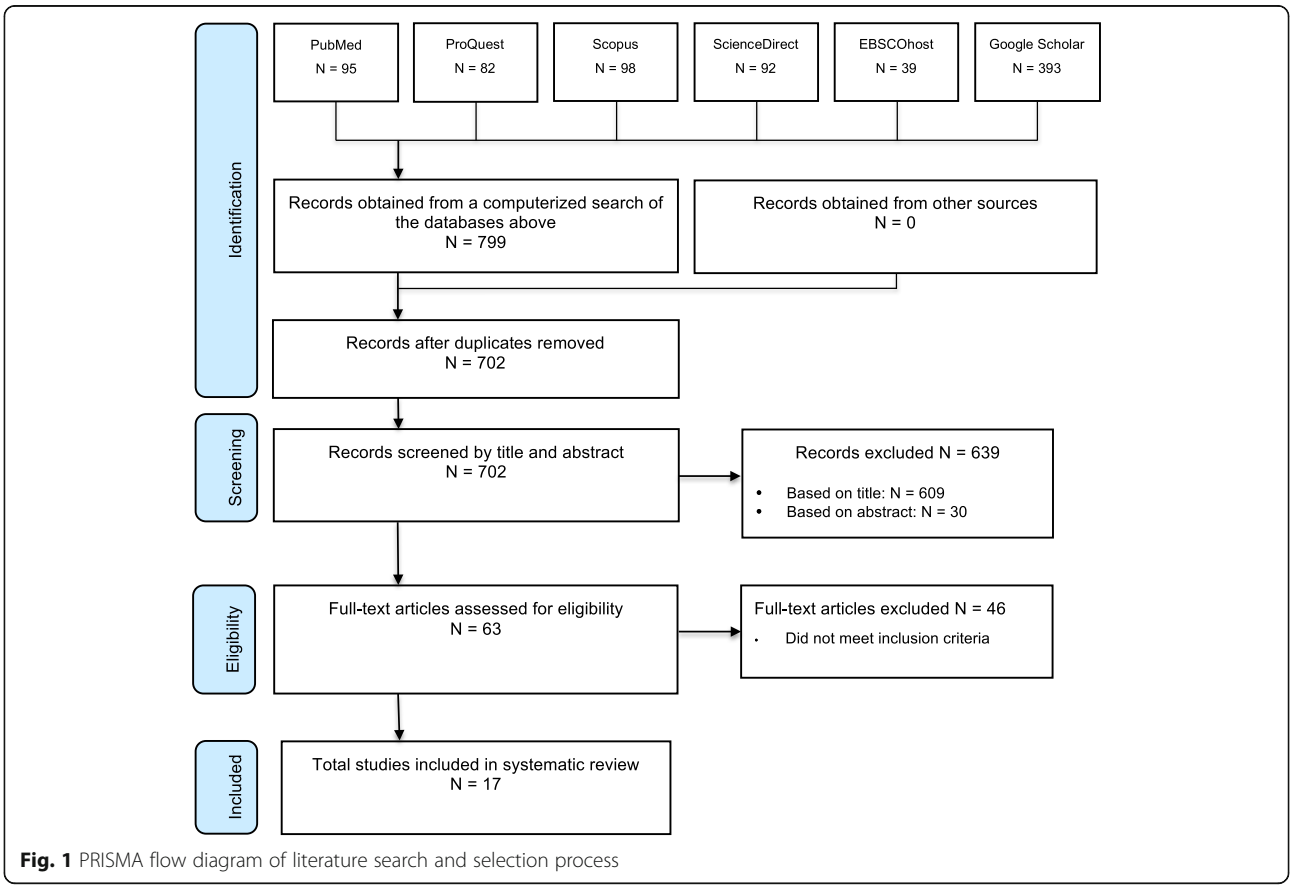

Fig. 1 PRISMA flow diagram of literature search and selection process

Study sample description

Participant numbers varied from 19 to 447. Six studies did not include a control group [8–10, 12, 18, 35]. Mean ages ranged from 28 to 54.7 years. Two studies included males only [35, 43]. Only one study [44] was conducted in Sub-Saharan Africa. Table 2 summarizes the sample characteristics of all participants, while HIV-specific sample characteristics are presented in Table 3.

Study design, aims and outcomes

Sixteen studies were cross-sectional, and one was a prospective cohort [9]. Study aims varied (Table 4), but all included objective measurement of balance and/or gait as part of the primary aim. Balance was assessed using both clinical and instrumented tests. All studies used timed clinical tests for assessing gait. No studies assessed gait kinetics or kinematics. Outcomes varied substantially. Table 5 (balance) and Table 6 (gait) present the outcomes assessed per study. Summaries of the results for individual outcomes are presented briefly in Table 7 (balance) and Table 8 (gait), and presented in more detail as additional files (see Additional file 1 for balance and Additional file 2 for gait).

Static balance Five studies assessed static balance using clinical tests. One study [45] assessed Romberg eyes-closed-on-foam and found the frequency of impairment to be higher in PLHIV. Tandem stance time was normal in PLHIV [21]. Four studies assessed single leg stance time [8, 9, 21, 22]. Impairments were noted either only with eyes closed, or with synergistic obesity, or when standing on the non-preferred leg (eyes open and closed).

One study [46] assessed COP sway path using a force plate, and found the incidence of increased values to be larger in advanced stages of infection and task difficulty. Sway velocity was examined by another study [47]. A significant increase was found in neurologically symptomatic PLHIV regardless of visual condition, and about 25% of PLHIV with asymptomatic HIV infection also demonstrated increased values.

Average velocity in anterior-posterior (AP) and average velocity in lateral (LAT) directions were assessed by one study [48]. PLHIV with asymptomatic HIV infection had significantly increased AP only in the eyes closed condition, while PLHIV with symptoms of chronic HIV disease had significantly increased AP both with eyes open and eyes closed, as well as significantly increased LAT (only with eyes closed).

Two studies [47, 48] assessed the coefficient of the preferential direction of movement (AP/LAT ratio) and found this to be normal in PLHIV. Romberg ratio of area (RA)

Table 1 Methodological quality appraisal

		Trenkwalder 1992 [46]	Arendt 1994 [47]	Beckley 1998 [50]	Bauer 2005 [7]	Dellepiane 2005 [48]	Simmonds 2005 [49]	Scott 2007 [35]	Richert 2011 [8]	Bauer 2011 [22]	Sullivan 2011 [21]	Erlandson 2012a [10]	Erlandson 2012b [18]	Cohen 2012 [45]	Beans 2013 [43]	Mbada 2013 [44]	Richert 2014 [9]	Erlandson 2014 [12]
1	Research question/ objective clearly stated?	N	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y
2	Study population clearly specified and defined?	N	N	N	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
3	Participation rate of eligible persons at least 50%?	CD	CD	CD	CD	CD	CD	CD	N	CD	CD	Y	Y	Y	Y	CD	N	CD
4	All subjects recruited from similar populations? Eligibility criteria pre-specified and applied uniformly?	NR	N	N	Y	NR	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
5	Justification of sample size?	N	N	N	Y	N	N	N	N	N	N	N	N	N	N	N	N	N
6	Exposure(s) measured prior to outcome(s)?[a]	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	N
7	Sufficient timeframe to see an association between exposure and outcome?[a]	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	N
8	Different levels of the exposure measured, as related to the outcome?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
9	Exposure measures clearly defined, valid, reliable, and implemented consistently?	NR	Y	Y	Y	NR	Y	Y	Y	Y	Y	Y	Y	Y	NR	Y	Y	Y
10	Exposure(s) assessed more than once over time?[a]	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	CD	N
11	Outcome measures clearly defined, valid, reliable, and implemented consistently?	CD	NR	NR	NR	CD	Y	Y	NR	Y	NR	N	N	N	Y	Y	NR	CD

Table 1 Methodological quality appraisal *(Continued)*

12	Outcome assessors blinded to exposure status?	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
13	Loss to follow-up after baseline ≤20%?[a]	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
14	Key potential confounders measured and statistically adjusted for?	N	N	N	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Total CAT score /14	1	3	3	7	2	6	7	6	6	6	7	7	7	7	7	8	6
	Total CAT %	7.14	21.43	21.43	50	14.29	42.86	50	42.86	42.86	42.86	50	50	50	50	50	57.14	42.86

Abbreviations: CD cannot determine, *NR* not reported

[a]Cross-sectional analyses provide weaker evidence than cohort studies regarding a potential causal relationship between exposures and outcomes. For cross-sectional analyses, the answer to Questions 6, 7, 10 & 13 should be "No". All studies were cross-sectional, except for Richert 2014 (prospective longitudinal cohort)

Table 2 Sample characteristics, all participants

Study ID	Country, setting	Serostatus & sample size (N)	Gender (%)	Age (years) (SD)	BMI (kg/m^2) (SD)	Edu-cation (years) (SD)	Recreational drug use/ Alcohol consumption/ smoking (N)	Depression/PN/Other co-morbidities
Trenkwalder 1992 [46]	Germany, NR	HIV+ 50	M 96 F 4	42.5 (9.3)	NR	NR	4 / NR / NR	NR/Yes/Various neurological deficits
		HIV- 50	NR	37.5 (11.0)	NR	NR	NR / NR / NR	NR / NR / Healthy
Arendt 1994 [47]	Germany, NR	HIV+ 46	M 74 F 26	ASX: 36.33 (9.18) SX: 38.8 (8.38)	NR	NR	0 / 0 / NR	NR / No / HIV type-1-related encephalopathy (n = 10)
		HIV- 38	M 53 F 47	37.7 (10.21)	NR	NR	NR / NR / NR	NR / NR / Healthy
Beckley 1998 [50]	USA, NR	HIV+ 9	M 89 F 11	38.9 (10.7)	NR	NR	0 / 0 / NR	NR / No / PGL (n = 2); Opportunistic infection (n = 3)
		HIV- 10[a]	M 50 F 50	34.3 (7.8)	NR	NR	NR / NR / NR	NR / No / Healthy
Bauer 2005 [7]	USA, outpatient infectious disease clinics	HIV+ 90	M 39 F 61	NRx: 40 (7.2) NNRTI: 40 (5.9) PI: 39 (6.4)	NR	NRx: 11.5 (1.6); NNRTI: 11.6 (1.7); PI: 12.1 (2.6)	Large % Hx of drug abuse/ NRx: 39.3%; NNRTI: 40%; PI: 35.1%/NR	NRx: 42.9%, NNRTI: 28%, PI: 35.1%/ NR/Exclusion criteria eliminated major psychiatric-, medical- & neurological disorders
		HIV- 78	M 47.4 F 52.6	38 (7.1)	NR	12.6 (2.2)	Large % Hx of drug abuse/ 16.7%/NR	17.9% / NR / Healthy
Simmonds 2005 [49]	USA, out- patient AIDS facility	HIV+ 100	M 78 F 22	40.70 (7.49)	NR	NR	NR / NR / NR	NR / No / Exclusion criteria eliminated major medical & neurological disorders
		HIV- 105[a]	M 37 F 63	44.9 (14.7)	NR	NR	NR / NR / NR	NR / No / Healthy
Dellepiane 2005 [48]	Italy, NR	HIV+ 30	M 40 F 60	ASX: 28 (NR) AIDS: 32.8 (NR)	NR	NR	NR / NR / NR	NR / NR / Alcoholic cirrhosis (n = 1); no neurological or oto-neurological symptoms
		HIV- 55	M 64 F 36	35 (NR)	NR	NR	NR / NR / NR	NR / NR / Healthy
Scott 2005 [35]	USA, HIV clinic	HIV+ 27	M 100	48.7 (6.5)	24.2 (4.1)	NR	NR / NR / NR	NR / NR / Exclusion criteria eliminated major medical & neurological disorders
Richert 2011 [8]	France, HIV clinics	HIV+ 324	M 80 F 20	[b]47.6 (41.8, 53.9)	[b]22.5 (20.6, 24.6)	NR	NR / NR / NR	NR / 14% / Hepatitis B: 7%, Hepatitis C: 19%
Bauer 2011 [22]	USA, outpatient infectious disease clinics	HIV+ 121	M 58 F 42	BMI < 21: 39.4 (1.0); BMI 21–29: 40.9 (0.8); BMI > 29: 37.6 (1.2)	<21(n = 35); 21–29 (n = 61); >29(n = 25)	NR	No differences between groups/ No differences between groups/NR	Significant differences (P < 0.05)/ NR/Exclusion criteria eliminated major psychiatric-, medical- & neurological disorders
		HIV- 86	M 49	BMI < 21: 38.5 (1.3);		NR		

Table 2 Sample characteristics, all participants *(Continued)*

			F 51	BMI 21–29: 38.0 (1.1); BMI > 29: 36.6 (1.0)	<21(n = 2); 21–29 (n = 30); >29 (n = 35)		No differences between groups/ No differences between groups/NR	Significant differences (P < 0.05)/NR/Healthy
Sullivan 2011 [21]	USA, HIV clinics, local community	HIV+ 40	M 70 F 30	41 (NR)	M 25.4 (3.34); F 26 (3.16)	M 14.1 (3.05); F 13.8 (2.67)	NR / No differences between groups/M 43%, F 20%	BDI: M 10.5 (8.33); F 12.8 (9.26)/M 26%, F 17%/NR
		HIV- 83	M 48 F 52	44 (NR)	M 26.9 (4.83); F 24.7 (4.49)	M 15.9 (2.27); F 15.3 (2.00)	NR / No differences between groups/M 10%, F 0%	BDI: M 2.08 (2.33), F 2.9 (3.08)/NR/Without medical or psychiatric conditions
Erlandson 2012a [10]	USA, Infectious Diseases Group Practice clinic	HIV+ 359	M 85 F 15	[b]50.8 (47.7, 55.7)	NR	NR	IDU (<1%), Cocaine (<1%), Marijuana (23%) / >7 drinks/wk. (4%) / Current: 34%	NR /NR/NR
Erlandson 2012b [18]	USA, Infectious Diseases Group Practice clinic	HIV+ 359	M 85 F 15	52 (0.3)	NR	NR	Current IDU (<1%) / >7 drinks/wk.: Non-fallers (4%), Single fallers (7%), Re-fallers (2%) / Non-fallers (30%), Single-fallers (42%), Re-fallers (47%)	NR/NR/30% reported ≥1 falls during the past year (of those, 61% were recurrent fallers)
Cohen 2012 [45]	USA, multiple clinical subsites	HIV+ 247	M 51 F 49	48.9 (8.9)	NR	NR	NR/No/NR	NR/NR/Exclusion criteria eliminated spinal injury, vestibular impairment, use of narcotics, antihistamines or sedatives within 48 h of testing
		HIV- 200	M 84 F 16	54.2 (11.2)	NR	NR	NR/No/NR	NR/NR/NR
Beans 2013 [43]	USA, Baltimore VA Medical Center	HIV+ 45	M 100	54.4 (6.3)	<25 (51.1%) ≥25 (48.9%)	NR	NR/NR/69.0%	NR/NR/Diabetes 26.7%, Hepatitis C 71.1%, Hypertension 68.9%, Chronic Pulmonary Disease 20%, Dyslipidemia 36.4%, Anemia 24.4%
		HIV- 27	M 100	54.7 (6.2)	<25 (32.4%) ≥25 (67.6%)	NR	NR/NR/56.8%	NR/NR/Diabetes 18.9%, Hepatitis C 55.6%, Hypertension 73%, Chronic Pulmonary Disease 29.7%, Dyslipidemia 25.8%, Anemia 37.8%
Mbada 2013 [44]	Nigeria, Virology Research Clinic	HIV+ 37	M 40.5 F 59.5	35.68 (7.71)	22.77 (4.17)	NR	NR/NR/NR	NR/NR/NR
		HIV- 37	M 40.5 F 59.5	35.73 (7.88)	24.31 (4.24)	NR	NR/NR/NR	NR/NR/Healthy
Richert 2014 [9]	France, HIV clinics	HIV+ 178	M 81 F 19	[b]48 (43, 56)	[b]22.2 (20.5, 24.5)	NR	Prior IDU (14%)/NR/NR	NR/NR/Cerebral CDC stage C condition: 3%, Hepatitis B: 7%, Hepatitis C: 20%

Table 2 Sample characteristics, all participants *(Continued)*

Erlandson 2014 [12]	USA, Infectious Diseases clinic	HIV+ 359	M 85 F 15	52 (5.2)	26.4 (6.0)	NR	Current IDU (<1%) /NR/NR	NR/NR/NR

Abbreviations: AIDS Acquired Human Immunodeficiency Syndrome, *ART* antiretroviral therapy, *ASX* asymptomatic, *BDI* Beck Depression Inventory, *BMI* Body Mass Index, *CDC* Centre for Disease Control, *DAST-10* Drug Abuse Screening Test, *F* female, *HAART* highly active antiretroviral therapy, *HIV* human immunodeficiency virus, *Hx* history, *IDU* intravenous drug use, *M* male, *MAST* Michigan Alcoholism Screening Test, *MDD* Major Depressive Disorder, *N* number of participants, *NA* not applicable, *NNRTI* non-nucleoside reverse transcriptase inhibitor, *NR* not reported, *NRTI* nucleoside reverse transcriptase inhibitor, *NRx* no treatment, *PGL* Persistent generalized lymphadenopathy, *PI* protease inhibitor, *PN* peripheral neuropathy, *SD* Standard Deviation, *SX* symptomatic, *USA* United States of America, *WR* Walter Reed stages

[a]Retrospective control group of healthy volunteers from previous study

[b]Median (IQR)

Table 3 Sample characteristics, PLHIV

Study ID	Disease staging	CD4 cell count, cells/mm^3 (SD)	Viral load (SD)	Treatment
Trenkwalder 1992 [46]	WR I-II (*N* = 17); WR III-V (*N* = 19); WR VI (*N* = 14)	NR	NR	NR
Arendt 1994 [47]	CDC II (*N* = 12); CDC III (*N* = 12); CDC IV C1 (*N* = 5); CDC IV C2 (*N* = 5); CDC IV D (*N* = 2); CDC IV B (*N* = 10)	NR	NR	NR
Beckley 1998 [50]	ASX (*N* = 2); CDC Stage A (*N* = 2); CDC Stage B (*N* = 2); CDC Stage C (*N* = 3)	Range 65–701; 5 participants had AIDS-defining CD4 counts (<200)	NR	Most were on zidovudine maintenance therapy
Bauer 2005 [7]	NR	NRx: 351 (282); NNRTI: 457 (375); PI: 320 (200)	*HIV burden × 1000 copies/ml:* NRx: 93.8 (163); NNRTI: 35.5 (102); PI: 20.1 (48.2)	NRx: *N* = 28; NNRTI: *N* = 25; PI: *N* = 37
Simmonds 2005 [49]	*Based on CD4 count* ASX (CD4 > 200) (*N* = 52); AIDS (CD4 < 200) (*N* = 48)	Range 189.83 (183.27) - 386.36 (302.39)	*Virions:* ASX 33545.25; AIDS 193401.00	NR
Dellepiane 2005 [48]	*CDC classification*ASX (*N* = 15); AIDS (group IV) (*N* = 15)	NR	NR	NR
Scott 2007 [35]	NR	408 (293)	*log copies/ml* 2.18 (0.94)	All were on a NRTI-based regimen, with 82% receiving a PI as a third agent
Richert 2011 [8]	CDC category C: 23%	[a]520 (348, 709)	<500 copies/ml: 83%	89%
Bauer 2011 [22]	NR	BMI <21: 280 (52); BMI 21–29: 422 (40); BMI > 29: 361 (64)	*Log10 viral load* BMI <21: 3.06 (0.34); BMI 21–29: 2.19 (0.26); BMI > 29: 2.08 (0.39)	*% no ART/NNRTI-based ART/ PI-based ART:* BMI <21: 38.2/26.5/35.3; BMI 21–29: 31.7/26.7/ 41.7; BMI > 29: 37.0/18.5/44.4
Sullivan 2011 [21]	NR	M 537.4 (258.97); F 583.4 (103.55)	M 13597.6 (4654.88); F 4609.7 (3226.36)	HAART: *N* = 25; Non-HAART: *N* = 6; NRx: *N* = 9
Erlandson 2012a [10]	NR	[a]551 (361, 768)	Detectable (≥48 copies/mL): 5%	NR
Erlandson 2012b [18]	NR	594 (16)	95% had plasma HIV-1 RNA < limits of detection	Any didanosine: Non-fallers: 57 (23); Single fallers: 10 (23); Recurrent fallers: 24 (36) Any stavudine: Non-fallers: 93 (37); Single fallers: 22 (51); Recurrent fallers: 33 (50) Efavirenz: Non-fallers: 86 (34); Single fallers: 10 (23); Recurrent fallers: 22 (33)
Cohen 2012 [45]	NR	556.4 (284)	*Log_{10}HIV RNA:* [a]3.50 (2.68, 4.42)	HAART: 76.9%
Beans 2013 [43]	NR	[a]445 (265, 531)	Non-detectable (<400 copies/ml): 91%	Majority were receiving cART
Mbada 2013 [44]	All: Clinical stage I of HIV/AIDS (ASX HIV infection, with PGL)	NR	NR	100% HAART
Richert 2014 [9]	CDC stage C 24%	[a]506 (340, 715)	HIV RNA level < 500 copies/ml: 84%	89% on ART
Erlandson 2014 [12]	NR	594 (303)	HIV-1 RNA < limits of detection: 95%	All participants taking effective cART

Abbreviations: AIDS acquired immunodeficiency syndrome, *ART* antiretroviral therapy, *ASX* asymptomatic, *BMI* Body Mass Index, *cART* combination antiretroviral therapy, *CDC* Centre for Disease Control, *F* female, *HAART* highly active antiretroviral therapy, *HIV* human immunodeficiency virus, *IQR* interquartile range, *M* male, *N* number of participants, *NA* not applicable, *NNRTI* non-nucleoside reverse transcriptase inhibitor, *NR* not reported, *NRTI* nucleoside reverse transcriptase inhibitors, *NRx* no treatment, *PGL* Persistent generalized lymphadenopathy, *PI* protease inhibitor, *PLHIV* people living with HI, *SD* standard deviation, *SX* symptomatic, *WR* Walter Reed staging
[a]Median (IQR)

as well as Way (average velocity of movement) was found to be increased in all HIV groups [48].

Sensory Organisation Test (SOT) sway strategy score was found to be lower (which is worse, as it indicates more reliance on the hip strategy as opposed to the ankle strategy) for bilateral stance (eyes closed) in PLHIV [22]. Two studies [7, 22] reported on SOT Equilibrium Quotient (EQ) and reported significant impairments in PLHIV during the most difficult SOT subtests (eyes closed or inaccurate visual input).

Table 4 Study aims

Study ID	Design	Aim
Trenkwalder 1992 [46]	Cross-sectional	To measure postural performance quantitavely in PLHIV (in different disease stages) versus seronegative controls, using a force plate.
Arendt 1994 [47]	Cross-sectional	To determine if stance control is impaired in early versus late HIV infection, using a force plate, and to compare results with the COG patterns in pyramidal or extrapyramidal disease.
Beckley 1998 [50]	Cross-sectional	To evaluate postural reflexes with EMG in PLHIV without obvious neurological disease, in order to determine whether postural reflexes are early markers of CNS involvement.
Bauer 2005 [7]	Cross-sectional	To assess sensorimotor function in PLHIV and seronegative controls.
Simmonds 2005 [49]	Cross-sectional	To characterize physical performance in PLHIV, and to examine group differences by pain and fatigue.
Dellepiane 2005 [48]	Cross-sectional	To investigate whether posturography can detect the presence of possible disorders of the vestibulo-spinal reflex.
Scott 2007 [35]	Cross-sectional	To determine the extent of neuromuscular activation of selected lower limb muscles of male PLHIV receiving ART, and its relationship to performance in clinical functional tests.
Richert 2011 [8]	Cross-sectional	To provide standardized assessments of locomotor function in PLHIV, focusing on lower limb muscle performance and balance, and on potential determinants of functional impairment.
Bauer 2011 [22]	Cross-sectional	To compare balance and gait in participants who differ in BMI and the presence or absence of HIV/AIDS.
Sullivan 2011 [21]	Cross-sectional	To investigate whether infratentorial brain volume would be marked by regional tissue shrinkage in PLHIV versus seronegative controls, and whether tissue deficits would be related to impairment in postural stability or psychomotor speed, using structural MRI and quantitative tests of postural stability, finger movement, psychomotor speed and dexterity.
Erlandson 2012a [10]	Cross-sectional	To compare the FFP, SPPB, and 400-m walk in PLHIV.
Erlandson 2012b [18]	Cross-sectional	To determine fall-rate and -risk factors among PLHIV by correlating fall history, medical diagnoses, and functional tests.
Cohen 2012 [45]	Cross-sectional	To determine whether PLHIV on HAART had an increased prevalence of vestibular disorders versus seronegative controls, using standard screening tests of vestibular and balance function.
Beans 2013 [43]	Cross-sectional	To compare locomotor function in male PLHIV versus seronegative controls, and test the association with aerobic exercise capacity.
Mbada 2013 [44]	Cross-sectional	To compare HRQOL and a performance-based measure of functional capacity between a homogenous sample of clinical stage I PLHIV versus seronegative controls.
Richert 2014 [9]	Prospective cohort	To prospectively assess the changes in locomotor function in PLHIV over time and to evaluate the determinants of variations in lower limb muscle performance.
Erlandson 2014 [12]	Cross-sectional	To assess the impact of physical function impairments on HRQOL in PLHIV using ART.

Abbreviations: *ART* antiretroviral therapy, *BMI* body mass index, *CNS* central nervous system, *COG* centre of gravity, *EMG* electromyography, *FFP* Fried's Frailty Phenotype, *HRQOL* health-related quality of life, *PLHIV* people living with HIV, *SPPB* Short Physical Performance Battery

Meta-analyses (Figs. 2 and 3) were performed for postural sway area [47, 48]. With eyes open, asymptomatic PLHIV and controls had similar sway areas, while PLHIV with symptoms of chronic HIV disease demonstrated a significant increase. Overall, sway area was significantly increased in PLHIV (combined group of those with and without symptoms of HIV). With eyes closed, PLHIV with asymptomatic HIV infection had normal sway areas, while PLHIV with symptoms of chronic HIV disease demonstrated a significant increase. Overall, sway area was increased in PLHIV.

Thus, the observed overall treatment effect in the combined group differed across the different subgroups. Homogeneity seems to exist between the sample estimates within the subgroups (I^2 = 0% for all groups), while a significant interaction existed between the subgroups (I^2 = 86.4% & 87.9% for the two outcomes, respectively), suggesting that the population parameters estimated by the subgroups are different. It should however be noted that the conjecture about homogeneity between sample estimates in these subgroup does not necessarily mean that the presence/absence of symptoms in PLHIV fully explains the heterogeneity observed across studies. In fact, the small number of studies and sample sizes for these outcomes might not provide adequate statistical power in demonstrating heterogeneity.

A meta-analysis (Fig. 4) was done for Romberg ratio of sway velocity (sway with eyes closed/sway with eyes open) [47, 48]. PLHIV with asymptomatic HIV infection had normal values, while PLHIV with symptoms of chronic HIV disease demonstrated a significantly larger Romberg ratio (which is worse as it indicates a higher amount of visual dependency). Overall, Romberg ratios were similar between the combined group of PLHIV and controls.

Substantial heterogeneity was found within the combined group (I^2 = 88%, p = 0.004 and I^2 = 91%, p = 0.00001, respectively). When splitting the subgroups according to presence of symptoms, PLHIV with asymptomatic HIV infection still showed evidence of high heterogeneity and non-significant results regarding impairment, while symptomatic

Table 5 Studies assessing balance outcomes

		Trenkwalder 1992 [46]	Arendt 1994 [47]	Beckley 1998 [50]	Bauer 2005 [7]	Dellepiane 2005 [48]	Simmonds 2005 [49]	Richert 2011 [8]	Bauer 2011 [22]	Sullivan 2011 [21]	Cohen 2012 [45]	Erlandson 2012a [10]	Erlandson 2012b [18]	Richert 2014 [9]	Erlandson 2014 [12]	Total studies assessing outcome
Balance outcome	Mean sway path (m/min)	X														1
	Sway velocity (m/s)		X													1
	Sway area (μVxs)		X			X										2[a]
	AP					X										1
	LAT					X										1
	AP/LAT quotient		X			X										2[b]
	Romberg ratio of sway velocity; RW		X			X										2[a]
	Romberg area of sway; RA					X										1
	Way					X										1
	SOT sway strategy score								X							1
	SOT EQ				X											1
	SOT number of falls; time before fall				X											1
	FBOS; LOS				X				X							2[c]
	Latencies of postural reflexes (ms)		X	X		X										3[a]
	Duration of postural reflexes					X										1
	Amplitude of postural reflexes					X										1
	Area of single EMG potential					X										1
	Normalized amplitude of ML-response			X												1
	Standardized LL Z-scores			X												1
	Romberg ECF (sec)										X					1
	Tandem stance (sec)									X						1
	Single leg stance time (sec)							X	X	X				X		4[d]
	Berg balance score							X								1
	TUG time (sec)							X						X		2[e]
	5STS time (sec)							X	X					X		3[f]
	5STS pace (rises/s)														X	1
	360° turn time								X							1
	Walk heel-to-toe (number of steps)									X						1

Table 5 Studies assessing balance outcomes *(Continued)*

Forward reach distance (cm)	X	X	2[g]

Abbreviations: 5STS 5-times sit-to-stand test, *AP* average velocity in an anterior-posterior direction, *cm* centimeters, *ECF* eyes-closed-on-foam, *EMG* electromyography, EQ equilibrium quotient, *FBOS* functional base of support, *LAT* average velocity in a medial-lateral direction, *LL* long loop, *LOS* limits of stability, *m* meters, *min* minute, *ML* medium loop, *ms* millisecond, *RA* Romberg area of sway, *RW* Romberg ratio of sway velocity, *sec* second, *SOT* sensory organization test, *TUG* timed-up-and-go test

[a]Meta-analysis performed

[b]Meta-analysis not done as Arendt 1994 does not report SD values

[c]Meta-analysis not done as Bauer 2005 does not report values for control group

[d]Meta-analysis not done due to heterogeneity in methodologies: Richert 2011 uses established normative values as comparison; Sullivan 2011 uses max time of 60 s, Richert 2014 has no comparison values

[e]Meta-analysis not done as Richert 2014 has no comparison group

[f]Meta-analysis not done as Richert 2011 & 2014 has no comparison groups

[g]Meta-analysis not done as Richert 2011 uses established normative values as comparison

Table 6 Studies assessing gait outcomes

		Bauer 2005 [7]	Simmonds 2005 [49]	Scott 2007 [35]	Richert 2011 [8]	Bauer 2011 [22]	Erlandson 2012a [10]	Erlandson 2012b [18]	Beans 2013 [43]	Mbada 2013 [44]	Richert 2014 [9]	Erlandson 2014 [12]	Total studies assessing outcome
Gait outcomes	Gait speed (m/s), preferred and/or fast					X	X	X			X	X	5[a]
	Timed gait (sec)	X	X						X				3[b]
	Cadence (time in sec for 5 steps), fast and preferred	X				X							2
	Gait initiation time (sec), fast and preferred					X							1
	6MWD		X	X	X				X	X	X		6[c]

Abbreviations: 6MWD 6-min walk distance, *m* meter, *sec* second

[a]Meta-analysis not possible as Bauer 2005 did not report mean results for gait speed and Richert 2014 included no comparison group or norm values

[b]Meta-analysis not possible as Bauer 2005 did not report mean for gait speed and Erlandson 2012a, 2012b & 2014 included no comparison groups or norm values

[c]Only 2 out of 6 studies included in meta-analysis, as Beans 2013 included men only, Scott 2007 & Richert 2011 & 2014 included no comparison groups or norm values (note heterogeneity between samples of the 2 studies included meta-analysis)

[d]Meta-analysis not possible, as Bauer 2005 did not report mean results for cadence or gait initiation time

Table 7 Summary of objective balance outcomes and results

Study ID	Results	Method of measurement	Outcomes assessed
Trenkwalder 1992 [46]	[b],[a]	4 conditions on force plate: Bilat stance EO + stable; Bilat stance EC + stable; Bilat stance EO + foam; Bilat stance EC + foam.	Mean sway path (m/min): EO & EC + foam[b] (all PLHIV except WR I-II)/EC + stable or foam[b] (all PLHIV)/All other conditions [a]
Arendt 1994 [47]	[b],[a]	2 conditions on force plate: Bilateral stance EO; Bilateral stance EC.	Sway velocity (m/s)[b] / AP/LAT quotient [a]
Beckley 1998 [50]	[b],[a]	Leg reflexes elicited in participants while standing upright on movable force plate - surface EMG recordings obtained from left tibialis anterior and medial gastrocnemius	Onset latencies (SL, ML and LL) (ms) / Normalized amplitude of ML[a]/LL-amplitude scaling (predictable [a]; unpredictable [b])
Bauer 2005 [7]	[b],[a]	1) SOT, 3 conditions: EO, EC, inaccurate visual input 2) Forward/backward lean tests 3) (Single-leg stance test)	1) SOT, for each condition: EQ. (EO[a], EC[b], inaccurate[a]) /Number of falls[a]/Time before a fall (seconds)[a] 2) FBOS (Lean amplitude/ft length)[b] 3) (Single Leg Stance time (s) - results not presented)
Simmonds 2005 [49]	[a]	Loaded forward reach Unloaded forward reach	Distance reached (cm)[a]
Richert 2011 [8]	[a],[c]	1) BBS 2) TUG test 3) FR test 4) SLS, EC 5) 5STS	1) Berg score[a] 2) TUG time (sec)[a] 3) Reach distance (cm)[a] 4) SLS time (sec)[c] 5) 5STS time (sec)[c]
Dellepiane 2005 [48]	[b], [a]	1) Static posturography: Romberg's position on force plate; EO & EC 2) Dynamic posturography: EO & EC; leg reflexes elicited via sudden tilts of moveable force plate, EMG recorded	1) Static: Way (EO & EC, SX[b]), Area, AP (ASX in EC[b], SX in EO[b] & EC[b]), LAT (SX in EC[b]), AP/LAT[a], RW, RA[b] 2) Dynamic (SL, ML and LL): Latency (SL: EO & EC, all HIV groups[b]) (ML: EO, SX, both legs[b]; EO, ASX, left leg [b]; EC, all groups[a]) (LL: EC, SX[b]; EC, ASX[a])/Duration (SL: EO, all PLHIV [a]; EC, SX, left leg[b]) (ML: EO, all PLHIV[a]; EC, all PLHIV, bilat[b]) (LL, EC, all PLHIV[b]) /Amplitude[a]/Area of single EMG[a]
Bauer 2011 [22]	[b], [a]	1) SOT, 3 conditions: EO, EC, inaccurate visual input 2) Forward/backward lean tests 3) SLS test 4) 360-degree turn test 5) 5STS test	1) SOT: Dependent variables calculated for each condition were: EQ (EC[b], inaccurate input[b]) Sway strategy score (EC[b]) 2) LOS (lean amplitude/ft length)[b] 3) SLST time (seconds) (only obese PLHIV, non-preferred leg[b]) 4) 360 deg. turn time (seconds) (only obese PLHIV[b]) 5) 5STS time (seconds)[a]
Sullivan 2011 [21]	[b], [a]	Walk-a-Line Battery. Conditions: Stand Heel-to-Toe; Walk Heel-to-Toe; and SLS.	1) Stand Heel-to-Toe time (seconds)[a] 2) SLS time (seconds) (non-preferred leg[b]) 3) Walk-Heel-to-Toe - number of steps out of 10 (EC[b])
Cohen 2012 [45]	[c]	Romberg tests on stable and on foam, 4 conditions: EO + stable, EC + stable, EO + foam, EC + foam.	Romberg time, EC + foam (seconds)[c]
Erlandson 2012a [10]	[c]	Tandem stand and 5STS as part of SPPB	5STS time (part of SPPB score)[c]/Tandem stance time (part of SPPB score)[c]
Erlandson 2012b [18]	[c]	Tandem stand and 5STS as part of SPPB	5STS time (part of SPPB score)[c]/Tandem stance time (part of SPPB score)[c]
Richert 2014 [9]	[c]	1) 5STS test 2) TUG test 3) SLS test	1) 5STS time (seconds)[c] 2) TUG time (seconds)[c] 3) SLS time (seconds)[c]
Erlandson 2014 [12]	[c]	5STS	5STS pace (rises/s)[c]

Outcomes included in meta-analyses are not included in this table

Abbreviations: 5STS 5-times-sit-to-stand, *AP* Average velocity in anterior-posterior direction, *ASX* asymptomatic; *BBS* Berg Balance Scale, *Bilat* bilateral, *COP* center of pressure, *deg.* degree, *EC* eyes closed, *EMG* electromyography, *EO* eyes open, *EQ* equilibrium quotient, *FBOS* functional base of support, *FR* functional reach, *LAT* average velocity in medial-lateral direction, *LL* long loop, *LOS* limits of stability, *ML* medium loop, *PLHIV* people living with HIV, *RW* Romberg index reported to way = ratio of way with EO & EC, *RA* Romberg index reported to area = ratio of area with EO & EC, *SL short loop*, *SLS* single leg stance, *SOT* sensory organization test, *SX* symptomatic, *TUG* timed-up-and-go

[a]no significant difference between PLHIV and controls

[b]PLHIV significantly impaired compared to controls or normative reference values

[c]No comparison provided/impairment quantified by reporting proportion of PLHIV with deficits

Table 8 Summary of objective gait outcomes and results

Study ID	Results	Method of assessment	Spatiotemporal outcome
Bauer 2005 [7]	[a]	8-m walk (preferred and fast)	Gait speed: time (sec) to cover distance[a] Cadence (time in sec for 5 steps)[a]
Simmonds 2005 [49]	[b]	50-ft (15.24-m) walk (preferred and fast)	Gait speed: time (sec) to cover distance[b]
Scott 2007 [35]	[b]	6MWD	Distance covered (m) in 6 min[b]
Richert 2011 [8]	[c]	6MWD	Distance covered (m) in 6 min[c]
Bauer 2011 [22]	[b]	8-m walk (preferred and fast)	Preferred[b] and fast gait initiation time (sec) Fast[b] and preferred gait speed (m/s) Fast and preferred cadence (time in sec for 5 steps)
Erlandson 2012a [10]	[c]	4-m walk as part of SPPB 400-m walk (fast)	Only presented as part of SPPB score Gait speed (m/s)[c]
Erlandson 2012b [18]	[c]	1) 4-m walk as part of SPPB 2) 400-m walk (fast)	1) Only presented as part of SPPB score 2) Gait speed (m/s)[c]
Beans 2013 [43]	[d,a]	1) 6MWD 2) 400-m long distance corridor walk	1) Distance covered (m) in 6 min[a] 2) Gait speed: time (sec) to cover distance[d]
Richert 2014 [9]	[b]	1) 6MWD 2) 10-m walk	1) Distance covered (m) in 6 min[b] 2) Gait speed (m/s)
Erlandson 2014 [12]	[c]	400-m walk (fast pace)	Gait speed (m/s)[c]

Outcomes included in meta-analyses are not included in this table
Abbreviations: 6MWD 6 min walk distance, *m* meters, *min* minutes, *sec* seconds, *SPPB* short physical performance battery
[a]No significant difference between PLHIV and controls
[b]PLHIV significantly impaired compared to controls or normative reference values
[c]No comparison provided/impairment quantified by reporting proportion of PLHIV with deficits
[d]Controls performed worse

PLHIV produced no evidence of heterogeneity (I^2 = 0%) whilst showing significant impairment for this outcome.

The high heterogeneity that exists particularly in the asymptomatic subgroup of PLHIV might be attributed to differences in the study populations used by the two studies. Differences existed in the sample sizes used (36 asymptomatic PLHIV in Arendt (1994) [47] versus only 15 in Dellepiane et al. (2005) [48]). Also, the age of the asymptomatic participants in these studies differed (mean of 36.33 versus 28 years). Finally, although both studies had similar definitions of "symptomatic" participants, only Arendt (1994) further classified the asymptomatic group into CDC disease stages.

Dynamic balance Both the Berg Balance Scale [8] and Timed-Up-And-Go (TUG) test [8, 9] were normal in PLHIV. For 5-Times-Sit-To-Stand (5STS) time, one study [22] found no group differences, while another [8] reported poor performance in PLHIV. The prospective cohort [9] reported an impaired 5STS time at baseline, and that 31% of PLHIV had a decline in performance over 1 year that was greater than the empirically defined threshold. Only

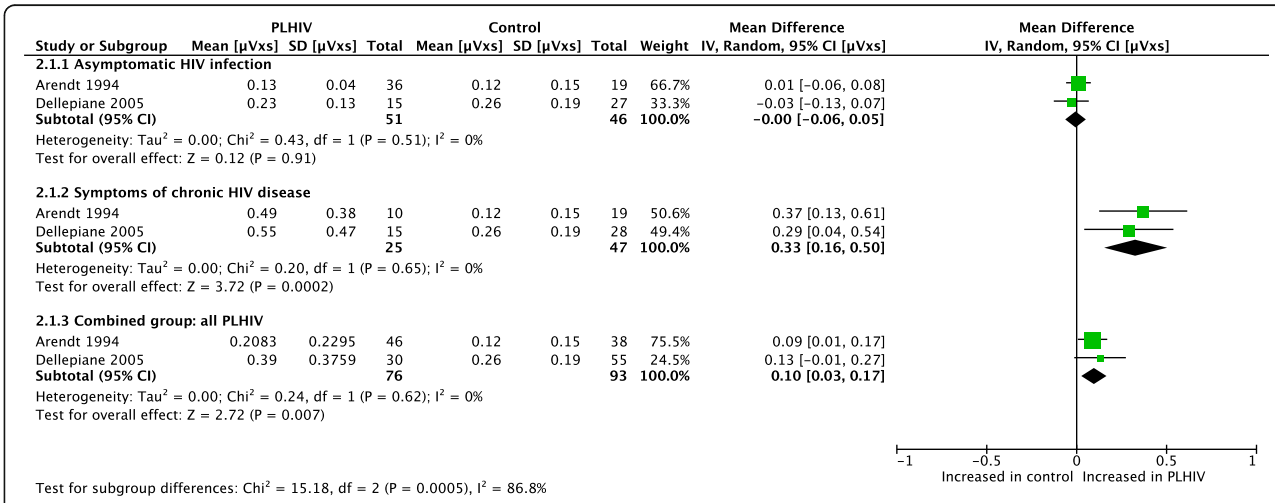

Fig. 2 Meta-analysis of sway area (μVxs) in PLHIV, eyes open

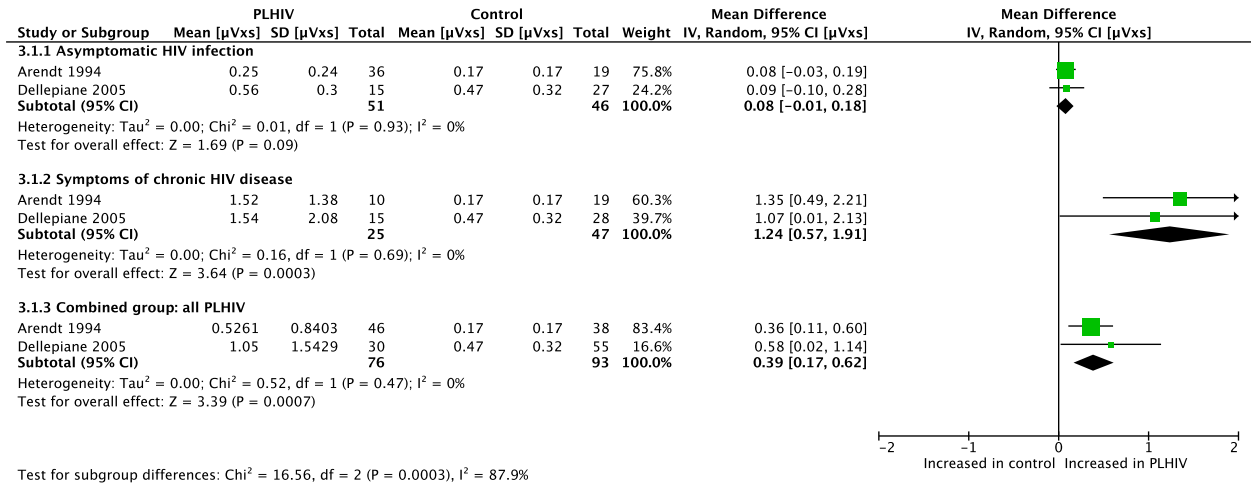

Fig. 3 Meta-analysis of sway area (μVxs) in PLHIV, eyes closed

PLHIV who were also obese performed worse in the 360-Degree-Turn test [22]. Walk-Heel-To-Toe was significantly impaired in PLHIV with eyes closed [21]. Two studies [8, 49] evaluated forward-reach distance, with no significant deficits noted.

The Functional Base of Support (FBOS) or Limits of Stability (LOS) tests were assessed by two studies [7, 22]; both reported significant impairments in all PLHIV.

Duration of postural reflexes was assessed by one study [48]. With eyes closed, there was a significant reduction for medium loop (ML) duration and long loop (LL) duration in all HIV groups. Amplitude of postural reflexes and area of single electromyography (EMG) potential were normal in PLHIV [48]. Neurologically intact PLHIV showed abnormal regulation of postural reflexes (LL amplitude scaling) under unpredictable, but not predictable, perturbations [50].

Meta-analyses were conducted for postural sway latencies [47, 48, 50] (Figs. 5, 6, 7, 8 and 9). For the left leg, short loop (SL) latencies for combined PLHIV groups were normal, with significantly increased values only in PLHIV with symptoms of chronic HIV disease upon further analysis. These findings were similar for the right leg. ML latencies, only assessed in two of the studies [48, 50] and only for the left leg, were significantly increased in combined PLHIV groups. In both legs, LL latencies were significantly increased in symptomatic, but not asymptomatic, PLHIV. The combined PLHIV group still showed a significant increase in LL latencies.

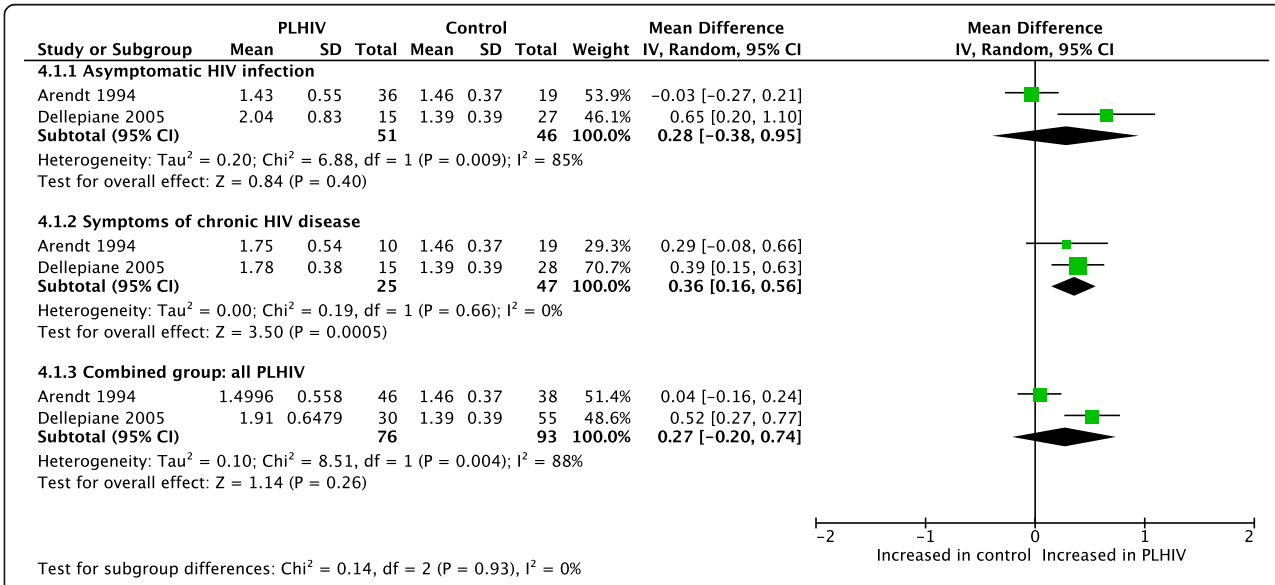

Fig. 4 Meta-analysis of Romberg ratio of sway velocity in PLHIV

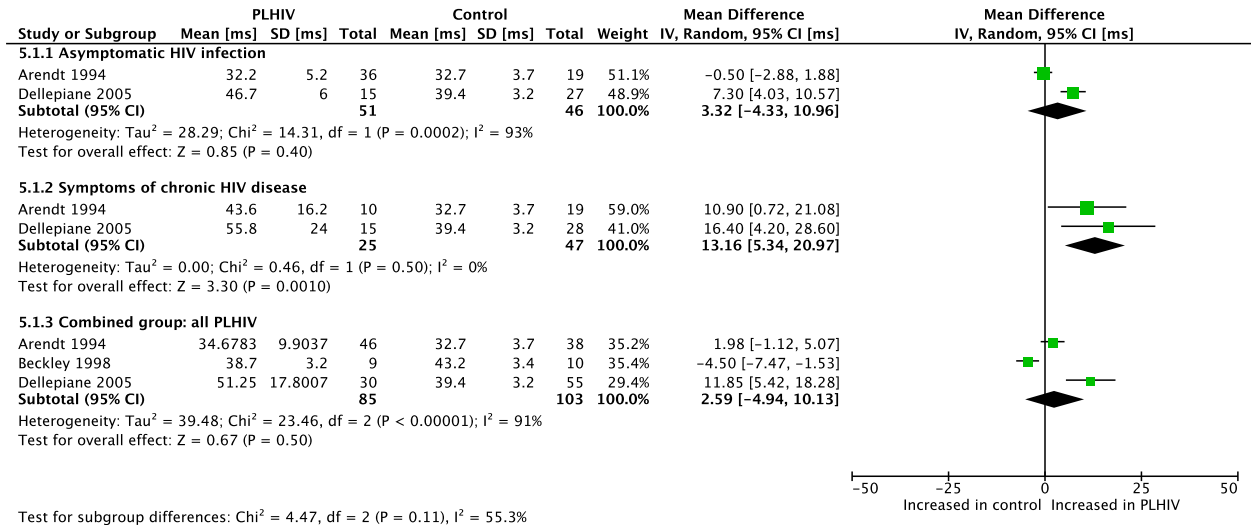

Fig. 5 Meta-analysis of left leg postural reflex latencies in PLHIV: short loop latencies (ms)

Gait Gait speed was assessed in eight studies [7, 9, 10, 12, 18, 22, 43, 49]. PLHIV demonstrated slowing of fast gait speeds [18, 43, 49]. One study [7] found no significant differences between PLHIV and controls, regardless of pace.

Meta-analysis [44, 49] (Fig. 10) indicated that 6-Minute Walk Distance (6MWD) was significantly shorter (worse) in PLHIV compared to controls. The likelihood of high heterogeneity in this meta-analysis should be considered (I^2 = 65%, p = 0.09) and might be due to the use of historical controls in one study [49] and differences in disease staging between the two studies. Among the un-pooled studies, three reported a decreased (worse) 6MWD [8, 9, 35], and one study found no impairment in PLHIV [43]. One study reported no impairments in PLHIV in cadence [7] and another reported that only PLHIV who were also obese were significantly impaired [22]. This study also reported that PLHIV had significantly delayed (worse) normal gait initiation time.

Falls One study [50] reported that fall incidence during unpredictable perturbations was similar in PLHIV versus controls. Similarly, another study [7] found no group differences in falls during SOT conditions. In contrast, one study reported a similar fall rate in middle-aged PLHIV (mean 52.0 years) and seronegative older adults (≥65 years) [18]. Impaired balance was a major associated factor. In addition, recurrent fallers had significantly slowed gait versus non-fallers. Furthermore, in a prospective cohort [9], it was reported that 12% of PLHIV experienced a minimum of one fall in the previous year. In PLHIV with recurrent falls, baseline 5STS time and 6MWD were significantly impaired, compared to non-fallers.

Measurement conditions and task difficulty Twelve studies included some form of increasing task difficulty, such as different visual input, stable versus unstable support surfaces, decreased base of support, predictable and unpredictable external perturbations, and walking at preferred versus fast gait speeds. Of these, nine (75%) demonstrated that both balance and gait impairments were more evident in more difficult task conditions, when comparing PLHIV to controls [7, 10, 18, 21, 22, 45, 46, 49, 50].

Disease severity Fifteen studies reported on the relationship between HIV-disease severity and locomotor performance. Of these, eight (53%) indicated a relationship between HIV-disease severity and impairments [7, 8, 10, 35, 46–48, 50]. In contrast, seven studies (46%) found no significant differences based on CD4 counts or viral loads [9, 21, 22, 43, 45, 49, 50].

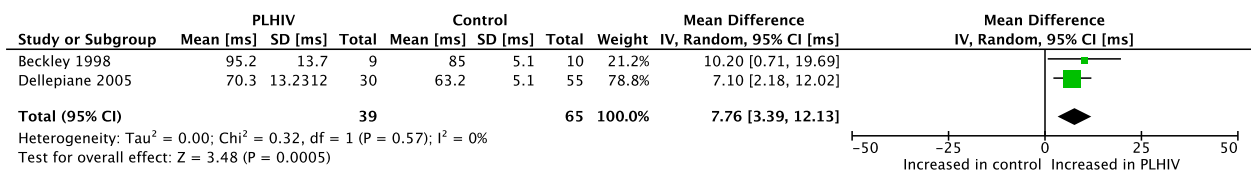

Fig. 6 Meta-analysis of left leg postural reflex latencies in PLHIV: medium loop latencies (ms)

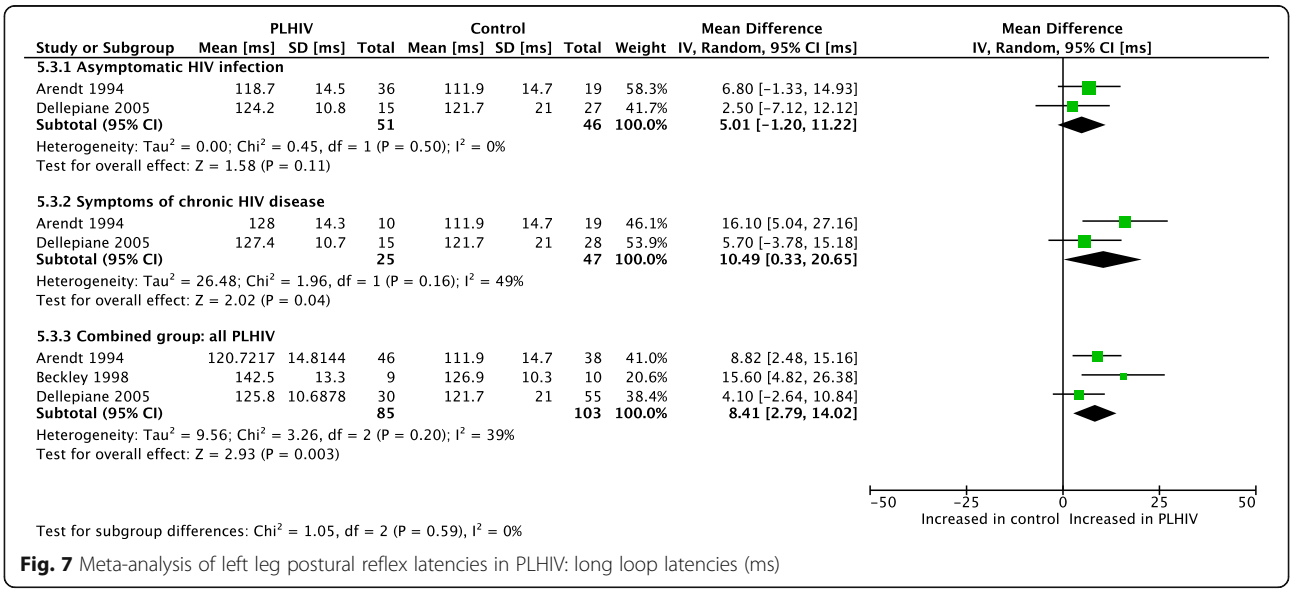

Fig. 7 Meta-analysis of left leg postural reflex latencies in PLHIV: long loop latencies (ms)

Treatment effects Seven studies reported on the relationship between ART and impairments in gait and/or balance, and none of these found any association [7–10, 21, 22, 35].

Peripheral neuropathy Five studies reported on the association between peripheral neuropathy and impairments in gait and/or balance in PLHIV, and none of these found statistically significant correlations between peripheral neuropathy and impairments of gait, dynamic balance or static balance [7, 8, 21, 46, 47].

Discussion

The aim of this review was to establish the current state of knowledge regarding objective impairments of gait and balance in PLHIV, and to emphasize those which could contribute to increased fall risk. To the authors' knowledge, this is the first work to do so. Our findings indicate that certain aspects of gait and balance are impaired in middle-aged PLHIV, resembling those proven to predict increased fall risk in elderly populations.

The methodological quality of articles ranged from fair to low, partly as a direct consequence of observational design. Earlier studies in particular had a high risk of selection bias due to omitting important information such as participant demographics and exclusion criteria. The psychometric properties of the different tests used to assess outcomes have not yet been evaluated in PLHIV; therefore, they cannot be assumed to be valid and reliable in this specific population. Balance and gait in PLHIV may be influenced by various factors apart from HIV-status.

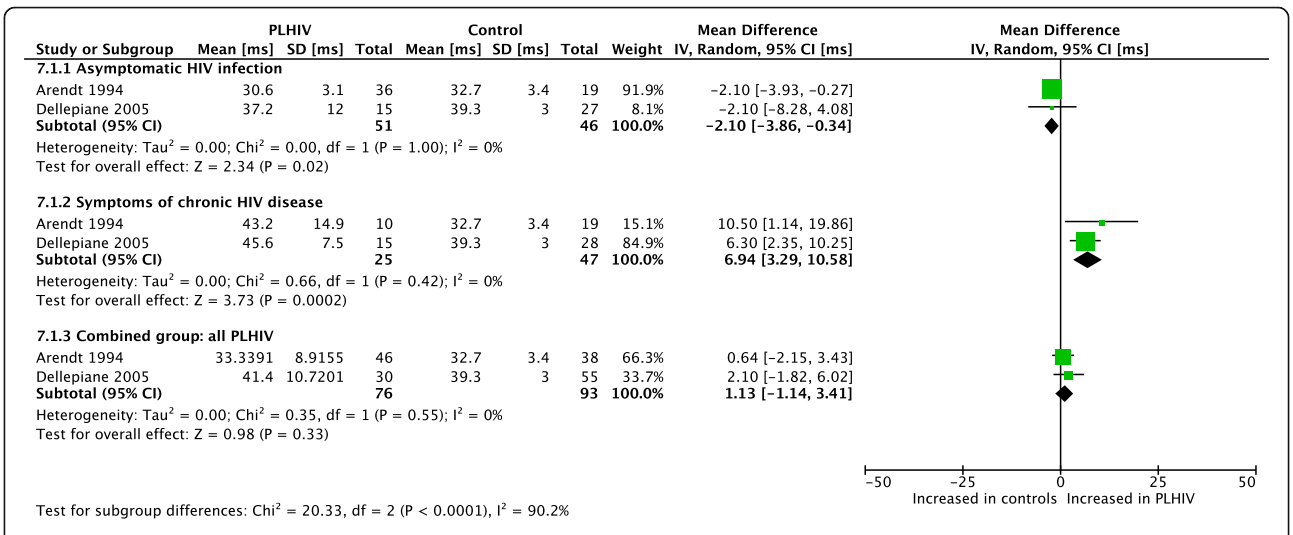

Fig. 8 Meta-analysis of right leg postural reflex latencies in PLHIV: short loop latencies (ms)

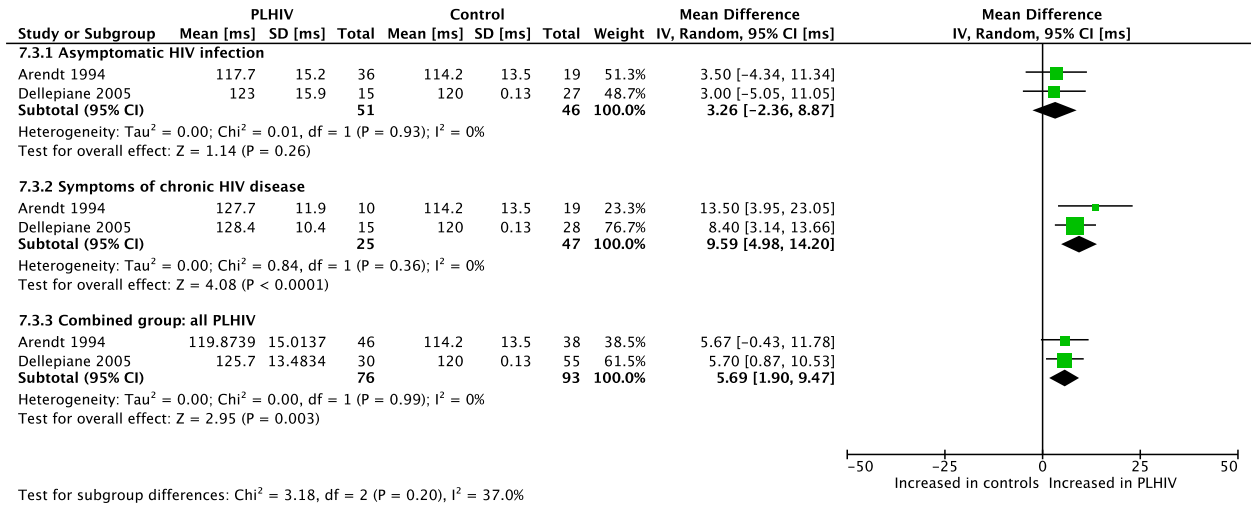

Fig. 9 Meta-analysis of right leg postural reflex latencies in PLHIV: long loop latencies (ms)

Although studies on average controlled and adjusted for many key confounders such as age, gender, BMI, markers of HIV and co-morbidities, very few reported on covariates such as level of education or adherence to treatment, and none on level of physical activity.

Various gait and balance parameters, including slowed gait speed [38], cadence [51], slowed gait initiation time [52] slowing of postural reflexes [53], and increased COP displacement and velocity [54] have been established to be associated with increased risk of falls in the elderly. Similarly, some of these variables are associated with risk of falls in PLHIV, namely slowed gait speed and impaired dynamic balance [18]. It has been reported that the best fall risk predictors in PLHIV are those proven to be predictors of fall risk in the elderly [18].

Static balance

Static balance is often quantified in terms of COP movement [55], which reflects neuromuscular control to keep the center of mass (COM) within the base of support's limits of stability [56–58]. Increased COP movement and velocity is associated with increased fall risk in the elderly [54]. In this review, evidence of increased postural sway or velocity was found in all studies evaluating these parameters, especially under challenging conditions [46–48], and was confirmed by meta-analyses. Impaired COP sway in PLHIV with asymptomatic HIV infection may suggest early involvement of postural control due to direct infection of the CNS by HIV. However, in neurologically symptomatic PLHIV, it cannot be assumed that anatomical structures or direct HIV-involvement of the CNS causes the observed deficits [46]. Lower limb muscle impairment might impair a person's ability to correct a shift in the body's COP to effectively prevent a fall [59]. In the elderly, it has been proposed that increased COP movement may be interpreted as an increase in hip abductor muscle activity to control postural stability on the medial-lateral direction [59]. It has also been suggested that decreased postural control with larger body sway increases tibialis anterior/soleus muscle co-activation, inducing the hip-strategy to preserve balance [60]. Greater co-activation may be partly be a compensation for decreased lower limb muscle strength and power [61]. As lower limb muscle impairments occur in PLHIV, this might contribute to the impaired COP parameters observed. HIV-associated vestibular dysfunction has also been reported [62]. Vestibular disorders have a deleterious effect on postural stability [63]. However, vestibular conditions are not characterised by impaired COP excursion, but rather by an increased frequency of movement, indicating poor control of COP [63].

A lower sway strategy score (the relative amount of high-frequency ankle versus low-frequency hip movement) for bilateral stance with eyes closed was found in PLHIV, albeit only reported in a single study in this review

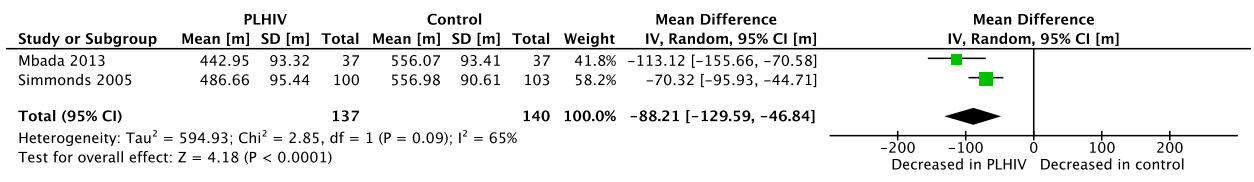

Fig. 10 Meta-analysis of 6-Minute Walk Distance (m) in PLHIV

[22], indicating a heavier reliance on the hip-strategy. In the general population, intact individuals will change their balance strategy from the normally employed ankle strategy, to relying on the hip strategy [56] when faced with more challenging conditions. Individuals with impaired balance, who already rely more heavily on the hip strategy, are less able to adapt to challenging conditions [56].

The SOT Equilibrium Quotient (EQ) is a calculation of the average COP sway, with lower EQ scores having been associated with increased fall risk in the elderly [64]. The two studies evaluating this outcome [7, 22] reported significantly lower EQ scores in PLHIV, especially with more challenging conditions.

Reduced single leg stance time is predictive of some (i.e. injurious), but not all, falls in the elderly [65]; however, the clinical value of this test might be called into question. The test might suffer from learning effects [66], leading to possible ceiling effects even in individuals with substantial impairment when only performed as a clinical test. Due to differences in the reporting of results among the included studies assessing this outcome, it is difficult to draw conclusions regarding impairment and the value of the test in PLHIV.

Dynamic balance

Dynamic balance is often assessed using dynamic posturography, which involves external perturbations being induced while a person tries to maintain an upright posture [56]. A common postural synergy in this scenario is the distal-to-proximal ankle strategy, involving a short loop (SL) and medium loop (ML) response in the gastrocnemius, followed by a long loop (LL) response in the tibialis anterior [67, 68]. Prolonged stance-stabilizing LL responses have been documented in elderly fallers [69]. Meta-analyses indicated that LL latencies were increased in symptomatic but not asymptomatic PLHIV, and upon combining all groups of PLHIV, LL latencies were still significantly increased. It is suggested that the early-observed prolonged LL latencies in PLHIV with asymptomatic HIV infection may indicate alterations in the central dopaminergic system (basal ganglia, caudatus nucleus and nigrostriatal system) [48].

Scaling of LL latency-amplitude, referring to the ability to adjust the size of posturally stabilizing reflexes and another important factor associated with falls [53], was assessed in one study [50]. Neurologically intact PLHIV showed abnormal postural reflex regulation under unpredictable, but not predictable, perturbations. Under random conditions, PLHIV automatically selected a LL response of a relatively similar size to one needed for medium perturbations. This response may not be sufficient to correct for large perturbations, leading to an increased risk of falling. However, the authors noted that the impairment in PLHIV was “mild” and did not appear clinically significant in early HIV infection.

The Limits of Stability (LOS) or Functional Base of Support (FBOS) test involves instrumented measurement of a forward leaning task and evaluates voluntary control of the center of gravity (COG). Instrumented LOS or FBOS, unlike the clinical Functional Reach test [8, 49], was impaired in PLHIV [7, 22]. Similarly, the Functional Reach test has been proven not to be an indicator for differentiating elderly fallers from non-fallers [70], while instrumented LOS is an early indicator of increased fall risk in the elderly [71]. These observations may be attributable to the differences in the task involved in the clinical versus the instrumented tests (although both assesses LOS) [71].

The 5STS test is an indicator of dynamic balance. Impaired performance was noted in two of the three studies evaluating this outcome [8, 9]. In addition to impaired central sensorimotor components being proposed to play a role [9], impaired 5STS time also implies poor lower limb muscle performance, which is associated with falls and disability both in HIV-seronegative elderly populations and in middle-aged PLHIV [8, 18]. Low appendicular muscle mass is prevalent in PLHIV and associated with functional impairment [72]. However, a decline in the ability of muscles to produce strength and power (dynapenia) might have a bigger contribution to functional decline in the elderly and is associated with poor chair-rise-time [73] Intra-muscular impairments, including fatty muscle infiltration, and low central activation are reported in PLHIV [29, 35, 74] and premature expression of genes associated with muscle aging is upregulated in PLHIV [75]. Grip strength might correlate with dynapenia in the elderly [76], and an accelerated decline in grip strength has been reported in PLHIV [77].

Owing to the dichotomous assessment by clinical tests of the ability to maintain standing balance, such tests only detect impaired balance once compensation strategies fail [56]. Selection of effective compensation strategies to restore balance (especially by persons who are physically active), might hide impairments, potentially hampering the use of such tests in active individuals or at an early stage of disease [56]. Level of physical activity was not assessed by any studies included in this review; ceiling effects in the results provided by the clinical balance tests can therefore not be excluded.

Although more suited to quantification of balance, interpretation of the results of instrumented posturography is complex. Generally, an increase in COP movement is assumed to reflect impaired balance; but this may not be true [78, 79]. Due to the interdependent relationship of the underlying systems, selection of an alternative compensation strategy to maintain stance could lead to observation of either increased or decreased COP movement, which in fact would reflect optimal balance control [56]. Second, altered COP movement can result from deterioration of several underlying systems. Thirdly, COP movement is affected by

training and learning effects, for example, individuals (and even more so those trained in sports) might be able to maintain a position very well, despite severe system deterioration, due to becoming familiar with the task or using selecting proper strategies for efficient compensation [56]. Results, especially from singular studies, must thus be considered cautiously and in the context of the assessment protocol, e.g. number of trials, and participant characteristics, such as activity level.

Gait

In this review, PLHIV exhibited impaired fast, but not preferred, gait speeds, despite being on successful HAART [10, 12, 22, 49]. PLHIV who were also recurrent fallers, had an even slower fast-paced gait [18]. Gait speed is reported as a predictor of falls in geriatric populations, with a linear relationship between slow gait speed and increased fall risk often assumed [80–82]. However, a non-linear relation has also been proposed [38]. Growing evidence show that gait and cognition, specifically attention and executive function [83] are interrelated. Neurocognitive decline occur in HIV [6, 13, 84–86], is in part associated with reduced dopaminergic function [87], and has been associated with slow gait speeds in this population [88]. Executive function, motor skills and attention/working memory are some of the domains that are affected by HIV [89]. Gait slowing is suggested to be an adaptive mechanism to prevent falls, to the effect that a slow gait speed might actually be associated with a reduced fall risk [38].

Six-Minute Walk Distance, which is actually an indicator of functional aerobic capacity, has been shown to correlate well with gait speed [90]. Meta-analyses of two studies [44, 49] suggests decreased 6MWD, and thus decreased gait speed under fast conditions, in PLHIV. Six-Minute Walk Distance was also reported to be decreased in PLHIV in the majority of un-pooled studies assessing this outcome [8, 9, 35] – however all of these studies used predicted values from the literature. This is of concern, as community-specific or cultural factors influence gait speed [43]. Gait initiation time was reported to be significantly slowed in PLHIV, albeit data from a single study [22]. Gait initiation time has been associated with increased fall risk in the elderly [52]. Cadence, which also has an association with gait speed and falls in the elderly [91], was assessed by two studies [7, 22], but owing to contradicting results, no firm conclusions can be drawn.

Measurement conditions and task difficulty

Evaluating performance under conditions of varying difficulty can provide more “real-life” insight into the quality of the specific underlying sensory systems [56, 92]. Studies assessing balance included in this review employed different sensory conditions, eliminating or disturbing the information of three main sensory systems. These included variations in visual input, different base-of support sizes and variations in support surfaces. For dynamic balance assessments, perturbations of varying amplitudes and predictability were induced using platform tilts. There was an overall tendency of PLHIV to perform similar to controls in easier conditions, and significantly worse with increased task difficulty. A correlation between static balance deficit and eyes closed conditions was demonstrated by clinical as well as instrumented tests [7, 22, 48]. Unstable conditions with eyes closed showed the greatest abnormalities in postural balance [45, 46]. Sullivan et al. (2011) [21] found impaired performance among PLHIV during clinical tests involving reduced base of support. Postural reflex synergies also appear to be task-dependent. Unpredictable perturbations resulted in worse dynamic balance performance [50]. It thus seems that PLHIV may have impaired response to unexpected perturbations or more complex tasks, predisposing them to falls. In the case of impairment of any of the systems contributing to postural balance, alternative compensation strategies are used by an individual to maintain postural control and orientation [56, 93]. Sensory reweighting comes into play, i.e. the nervous system will rely on more accurate sensory input, rather than less accurate, conflicting information [94]. Individuals relying more on one particular balance system are thus less able to adapt to situations where input to that system is disturbed, and have to rely on only the remaining systems [56]. This sensory reweighting seems impaired in PLHIV. Also, impaired dual-task performance has been demonstrated in PLHIV [95], although none of the included studies assessed this condition.

All gait tests in included studies were conducted on level, unobstructed walkways. During walking, many falls occur not during normal walking, but rather when negotiation challenging terrains. Results might have been more clinically relevant had irregular or unfamiliar surfaces been assessed, especially since dynamic balance in PLHIV seem to be more impaired under challenging circumstances. However, both self-selected and fast gait speed conditions were evaluated, with group differences mostly found when comparing fast gait. It has been suggested that walking at different speeds likely influences both the noise level in human motor performance as well as dynamic error corrections [96]. Thus, impairments at fast paced conditions may indicate deficits under more challenging conditions.

Disease severity

A dose–response relationship between HIV disease severity and locomotor impairment was suggested in 53% of studies. In addition, subgroup analyses highlighted impairments in postural reflex latencies that were inconspicuous in a combined group of all PLHIV, but became apparent in only those with symptoms of chronic HIV disease when compared to controls. However, methodologically it remains a

challenge to attribute observed differences between PLHIV and controls directly to HIV infection, as evident from the discussion thus far. Comparison populations most likely always differ in terms of many confounding factors [8]. It cannot be assumed with certainty that observed impairments are purely related to severity of HIV infection, and the contribution of various comorbidities and opportunistic infections should be considered. This is especially true for the older studies, where eligibility criteria did not control for various confounders and comorbidities.

Treatment effects: Antiretroviral therapy (ART), combination antiretroviral therapy (cART) or highly active antiretroviral therapy (HAART)

The majority of studies reporting on treatment effect failed to find significant associations to balance or gait outcomes in PLHIV, regardless of the different combinations of drugs (terms used for combination use of ARV including ART, cART or HAART). Thus, antiretroviral therapy does not appear to be a reversing factor with regard to locomotor impairments.

Peripheral neuropathy

None of the five studies reporting on the association between peripheral neuropathy and locomotor impairments found any significant relationships. A possible explanation for balance abnormalities among PLHIV, at least for those parameters measured by the included studies, might thus indicate involvement of the central rather than peripheral nervous system [7, 8, 21, 46, 47]. The fact that eyes closed conditions were often necessary to elicit group differences in balance, further motivates CNS dysfunction as an underlying mechanism [7]. It is reported that deficits in infratentorial brain tissue volume and disruption of the pontocerebellar fiber system microstructure, at least in part, may contribute to locomotor impairments in PLHIV [21]. It can, however, not be concluded with certainty that no association exists between gait or balance and peripheral neuropathy in PLHIV. It is possible that peripheral neuropathy adversely affects gait and balance parameters that were not measured in these studies. For example, impairments in joint kinematics (assessed by none of the included studies in this review) have been associated with peripheral neuropathy in Type 2 diabetic patients [97].

Implications for future research

While the importance of identifying spatiotemporal deficits is acknowledged, the associated kinematic and kinetic data can provide more insight into underlying mechanisms of the observed impairments. Some locomotor impairments related to early functional decline might be too small to be detected by visual observation alone in the clinical setting [51, 98]. These subtle impairments may however have substantial consequences for the individual. Thus, there is a need for more robust quantitative assessment, such as three-dimensional biomechanical motion analysis. We also suggest the use of dual tasking in PLHIV to assess the subtler changes in function, and adding more challenging conditions to gait assessments. Furthermore, a need exists for higher quality research. Carefully selected, representative samples will make results more homogeneous, relevant and generalizable. In addition, valuable information can be extracted from the geriatric literature that is likely to inform research in PLHIV, especially with regards to data on falls and specific movement impairments. This should be further explored, and the psychometric properties of both instrumented and clinical gait and balance assessments should be determined specifically in PLHIV. Lastly, we found the lack of studies conducted in Sub-Saharan Africa, the epicenter of the HIV epidemic, surprizing. More research is needed in developing countries to address this gap.

Review limitations

Language bias is likely in this review, as only studies published in English were considered. Another limitation of the review is that only two included articles were appraised by more than one reviewer, meaning that fifteen of the seventeen articles were scored for methodological quality by only one reviewer. In addition, ceiling effects might have hampered results from clinical tests. No studies in this review measured COM movement, with a subsequent incomplete representation of balance in PLHIV at present. Results of this review should be interpreted with caution as substantial statistical heterogeneity existed between the included studies, albeit expected, as evident in the meta-analyses (indicated by high I^2 values). Due to the small number of studies per outcome, all sources of heterogeneity could not be accounted for, but some possible explanations for variation in results have been discussed. Clinical heterogeneity was evident in the majority of studies, particularly in terms of setting, sample sizes, age groups, gender distributions, and HIV-staging. A wide variety of study outcomes and measurement methods were used. Given the paucity of research on existing impairments and the optimal method of evaluating these in PLHIV, the wide variation in assessment tests used was to be expected. Although the diversity in populations, especially regarding disease definition and subgroups, might seem surprising, it must be kept in mind that HIV classification systems have evolved substantially since the earliest included study and that HAART regimes did not yet exist in those earlier periods. Furthermore, publication- and reporting biases are suspected in this review, due to many authors collaborating on different papers and the same populations possibly used in different studies. However, formal assessment using funnel plots was not possible due to the low number (<10) studies assessing a similar outcome.

Conclusions

This review found that young to middle-aged PLHIV have impairments in certain aspects of gait and balance, which are similar to those that predispose elderly seronegative populations to falls. The impairments are more pronounced during challenging conditions, might be associated with HIV disease severity, are not influenced by ART, and might not necessarily be associated with peripheral neuropathy. Results should be interpreted with caution due to the overall fair to low methodological quality, substantial heterogeneity and many outcomes being assessed by singular studies only. The effect of HIV on gait and balance parameters, and in particular biomechanical outcomes, are currently insufficiently quantified and this review provides a first step to inform future research. Further investigation involving more methodological uniformity is warranted to better identify and understand relevant locomotor impairments in PLHIV. Only then can more clinically relevant conclusions, such as appropriate strategies for fall-prevention in this population, be drawn.

Additional files

Additional file 1: Results for objective balance outcomes in PLHIV (un-pooled dependent variables). Detailed summary of individual balance outcomes assessed across studies (DOCX 53 kb)

Additional file 2: Results for objective gait outcomes in PLHIV (un-pooled dependent variables). Detailed summary of individual gait outcomes assessed across studies (DOCX 101 kb)

Abbreviations

5STS: 5-Times-Sit-To-Stand; 6MWD: Six-Minute Walk Distance; AIDS: Acquired Immune Deficiency Syndrome; AP: Average velocity in an anterior-posterior direction; ART: Antiretroviral therapy; ASX: Asymptomatic HIV infection (clinically latent phase of HIV); BMI: Body Mass Index; cART: Combination antiretroviral therapy; CD: Cannot determine; CDC: Centre for Disease Control; CI: Confidence interval; CNS: Central nervous system; COG: Center of gravity; COM: Center of mass; COP: Center of pressure; EC: Eyes closed; EMG: Electromyography; EO: Eyes open; EQ: Equilibrium Quotient; F: Female; FBOS: Functional Base of Support; FFP: Fried's Frailty Phenotype; GIT: Gait initiation time; HAART: Highly active antiretroviral therapy; HIV: Human Immunodeficiency Virus; HRQOL: Health-related quality of life; JB: Jochen Baumeister; KB: Karina Berner; LAT: Average velocity in a medial-lateral direction; LL: Long loop; LM: Linzette Morris; LOS: Limits of Stability; M: Male; MeSH: Medical Subject Heading; ML: Medium loop; ms: Milliseconds; N: Number of participants; NA: Not applicable; NIH: National Institutes of Health; NNRTI: Non-Nucleoside Reverse Transcriptase Inhibitor; NR: Not reported; NRTI: Nucleoside Reverse Transcriptase Inhibitors; NRx: No treatment; PI: Protease Inhibitor; PLHIV: People living with HIV; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; QL: Quinette Louw; RA: Romberg ratio of area; SD: Standard deviation; SL: Short loop; SOT: Sensory Organisation Test; SPPB: Short Physical Performance Battery; SX: Symptomatic (presenting with various symptoms of chronic HIV disease); TUG: Timed Up-And-Go; WR: Walter Reed staging

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Availability of data and materials

The study data extracted for analyses in the current publication are available from the corresponding author on reasonable request.

Authors' contributions

KB and QL conceptualized the review and analysed the data. In addition, KB searched the databases, extracted the data, performed critical appraisal, analyzed the results and wrote the manuscript. QL assisted in designing data extraction sheets and analyzing the data. QL, LM and JB assisted in interpreting results and revising the manuscript. QL served as a second reviewer for consultation during the screening of articles for inclusion. LM served as a second reviewer in critically appraising two randomly selected articles. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Consent for publication

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Competing interests

The authors declare that they have no competing interests.

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